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THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

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A CLINICAL STUDY OF RADIATION CATARACTS AND THE RELATIONSHIP TO DOSE*

By GEORGE R. MERRIAM, JR., M.D., *and* ELIZABETH F. FOCHT, B.A.
NEW YORK, NEW YORK

THE radiation cataract problem has interested numerous workers since the original experimental work of Chalupecky in 1897.[1] The early investigative work has been reviewed by Desjardins[8] and Poppe.[25] In recent years, interest in this complication of therapy has increased considerably, particularly with the development of higher energy equipment and the expanding work with radioactive materials. A great deal of experimental work has been done on animals in an effort to determine the dose of various qualities of radiation that will produce a cataract, the manner and rapidity with which the opacity develops, the pathologic and metabolic changes that result and other related problems. The work of such investigators as Poppe,[25] von Sallmann, *et al.*[32–38] Cogan, *et al.*,[3–5] Kinsey,[15–17] Evans,[9,10] Leinfelder and co-workers,[19,20] Upton, *et al.*,[30–31] Nordmann and Mandell[24] and others should be consulted regarding these aspects of the problem.

The underlying stimulus for this investigative work is the fact that so little is known about radiation cataracts in humans. The clinical appearance was originally described by Rohrschneider,[27] and more recently by Cogan, Donaldson and Reese,[6] and is now well established. According to Cogan and his group,[6] the characteristic features of a radiation cataract are the initial opacity which ophthalmoscopically appears as a dot and is usually situated at the posterior pole. As this enlarges, small granules and vacuoles appear around it. The central opacity becomes larger and develops a relatively clear center giving it a doughnut shaped appearance. The whole opacity is now 3 to 4 mm. in diameter. At about this same time, granular opacities and vacuoles may appear in the anterior subcapsular region, usually in the pupillary area. When the lens is examined with the slit lamp biomicroscope, the initial opacities appear granular and have a yellowish hue. The central posterior opacity gradually splits parallel with the plane of the capsule forming a bivalve configuration. The opacity may remain stationary at any stage. Frequently, it progresses slowly over a considerable period to the point described and then remains

* From the Head and Neck Service and the Physics Department of the Memorial Center, New York City, and the Institute of Ophthalmology, Columbia-Presbyterian Medical Center, New York City. Presented at the Thirty-seventh Annual Meeting of the American Radium Society, Washington, D. C., April 21–23, 1955.

stationary. If it continues to progress, it becomes nonspecific and cannot be differentiated from other types of cataracts.

In the early stages a radiation cataract is fairly characteristic, but not entirely so. Lens opacities of a somewhat similar type are seen in patients with retinitis pigmentosa and in complicated cataracts that occur with endogenous ocular and systemic diseases and, occasionally, without any known cause. However, a careful history and ocular examination will usually enable a differential diagnosis to be made with considerable accuracy. The clinical findings are generally more accurate than the histologic manifestations, according to Cogan and his group.[6]

General times of onset have been given from the reported cases but not in relation to the many variables such as the quality of radiation and the dose or duration of treatment. Furthermore, the essential problems of the minimum dose that will produce a lens opacity, the incidence of cataracts at various dosage levels with varying methods of treatment, the relative effects of single and divided treatments, the effect of dose and duration of treatment on the time of onset of a cataract, the effect of dose on the incidence of stationary or progressive opacities, the effect of the quality of radiation, and the relative sensitivity of young and adult lenses still remain unsolved.

There have been approximately 81 cases of radiation cataracts in humans due to roentgen or gamma radiation reported in the literature to date.[2,7,14,18,21,23,28,29] However, in only 13 of these is the dose given or the radiation factors stated so that it can be calculated. Leinfelder and Kerr[21] reported two cataracts in patients whose lenses received over 1,400 r (200 kv. in 3 weeks). Hunt[14] reported a total of 5 cases—2 from roentgen rays and 3 from radium. In the 2 roentgen ray cases one lens received a dose of over 4,500 r and the other 775 r with 130 kv. roentgen ray. The treatment time was not specified. His smallest calculated dose to the lens in the radium patients was 1,350 r. In another of his radium cases (Case IV) Hunt stated that one eye developed a cataract 8 years after treatment and his calculated dose to the lens was 2,400 r in 5 days. The fellow eye in this patient subsequently developed an opacity 8 years after treatment but no estimate of the dose is given. Schulz and Heath[29] reported a lens opacity which developed in an eye exposed to 1,200 r, but no factors or treatment time are given. Cogan and Dreisler,[7] in the most recent report, found a radiation cataract in 1 of 3 patients whose lenses received 600 r (200 kv. delivered in 2 days). They reported 4 other cases—1 with a dose at the lens of 800 r at 200 kv. in one month, a second with a dose of 1,000 r in 3 weeks at 200 kv., a third with 2,400 r in a single treatment at 200 kv. and the fourth with 2,400 r in 10 days at 1,200 kv. Ham,[13] in a recent review article, has suggested that 500 r of roentgen or gamma rays be regarded as potentially dangerous to the human lens, although no mention is made of the duration of treatment. In respect to the dose that will produce a cataract this is the extent of our knowledge up to the present time.

At the Second Conference on Radiation Cataracts held by the National Research Council in 1950, a report was made on a group of patients who developed lens opacities following treatment with roentgen rays of varying energies or radium.[22] The minimum calculated dose to the lens, in the patients studied at that time, was given as 1,500 r with roentgen rays. In this present study these and additional patients have been measured by the method to be described. As will be seen, many patients have since been found in whom the minimum dose was considerably lower than that previously reported.

PLAN OF INVESTIGATION

The purpose of this study has been to collect as large a series of radiation cataracts as possible, actually measure the amount of radiation to the lens and to analyze the available data to gain informa-

tion concerning the following problems: (1) the minimum dose to the lens that will produce a cataract; (2) the percentage incidence of cataracts at increasing dosage levels; (3) the effect of dose on the time of onset of a cataract; (4) the effect of dose on the incidence of stationary or progressive opacities; (5) the relative effects of single and divided treatments on the above; and (6) the relative sensitivity of young and adult lenses.

During the past 30 years a large number of radiation cataracts have been seen in the Head and Neck Service of the Memorial Center, New York City. In 1939, Reese[26] reported on the operative treatment of such cases, but no attempt was made to estimate the dose that produced them. Some of the cases reported in his series are in this study, but many are not, since the radiation factors used in the early cases could not be reduplicated.

During the past 10 years the files of the Memorial Center, New York City, have been searched back to 1925, as well as the records of the Radiotherapy Department of the Institute of Ophthalmology, Columbia Presbyterian Medical Center, New York City, which was started in 1947. A total of 100 cases of radiation cataract was found in which the radiation factors could be reduplicated. In every instance the eyes were examined by an ophthalmologist* and the diagnosis established by means of the ophthalmoscope or the slit lamp biomicroscope. Approximately one quarter were examined by the last method. Cases which did not have an ocular examination, or in which the etiology was in question due to some complicating factor (previous surgery, trauma, hemorrhage or uveitis), or for which the dose to the lens could not be determined were excluded from this group. Also excluded were cases with early peripheral dots or vacuoles which occurred in elderly patients where the possibility of early senile changes made an accurate diagnosis of radiation changes uncertain. Such early changes when found in children were included if the other lens were clear and there were no other complicating factors.

In this study a radiation cataract is any clinically recognizable opacity having the characteristic appearance previously described, irrespective of whether or not vision was affected.

In addition to the cases with radiation cataracts, 73 cases were found all of which had had irradiation to the head but which did not develop lens opacities.† All of these patients had eye examinations from 3 years, 1 month to 28 years, 6 months after completion of treatment. Patients with eye examinations less than 3 years after therapy were excluded. The average time of the last ocular examination after therapy was 8 years, 11 months. For this study, therefore, there was a total of 173 cases (100 with radiation cataracts and 73 without lens opacities).

The actual amount of radiation to the lens for each case has been measured by the method to be described. The cases are listed in Tables I and II in which are shown the age and sex of the patient, the condition for which treatment was given, the treatment factors, the dose of radiation to the lens, the duration of treatment, the time after treatment when the cataract was first seen, whether the lens opacity was stationary or progressive and the length of the follow-up. Most of the figures in Tables I and II have been rounded off to the nearest 50 for the highest doses. In Figure 8 they were left as measured in order to show the individual cases more clearly.

In Table I the dose is given as over 1,500 r in a few of the cases. Where part of the treatment was given with the radium pack, a discontinued 4 gm. teletherapy unit, measurements could not be made. However, the dose from the other methods of

* Many of the cases were examined by Dr. A. B. Reese, New York, New York.

† An additional group of 52 cases which had radiation to the head and which had no symptoms of impaired vision 5 years or longer after completion of treatment was also examined. These have been excluded since they did not have eye examinations. It is interesting, however, that they did not alter the percentage incidence.

TABLE I

RADIATION CATARACTS

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time Cataract First Seen	Progressive or Stationary	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium					
SINGLE TREATMENT											
1	53	M	Basal cell carcinoma of lid			Plaque	200	Single	22 yr. 1 mo.	Stationary	22 yr. 1 mo.
2	54	F	Basal cell carcinoma of nose			Plaque	200	Single	19 yr. 2 mo.	Stationary	19 yr. 2 mo.
3	77	M	Basal cell carcinoma of face			Plaque	300	Single	2 yr. 6 mo.	Indeterminate	3 yr. 8 mo.
4	62	M	Basal cell carcinoma of cheek			Plaque	350	Single	2 yr. 11 mo.	Stationary	9 yr. 7 mo.
5	63	M	Basal cell carcinoma of lid			Plaque	500	Single	8 yr. 3 mo.	Progressive	15 yr. 10 mo.
6	45	F	Basal cell carcinoma of lid			Plaque	500	Single	8 yr. 7 mo.	Stationary	16 yr. 2 mo.
7	63	M	Basal cell carcinoma of nose			Plaque	550	Single	8 yr. 7 mo.	Progressive	8 yr. 7 mo.
8	55	F	Basal cell carcinoma of face			Plaque	650	Single	4 yr. 2 mo.	Progressive	17 yr.
9	64	F	Basal cell carcinoma of face			Plaque	650	Single	4 yr. 5 mo.	Stationary	13 yr. 9 mo.
10	54	F	Basal cell carcinoma of nose			Plaque	650	Single	5 yr. 6 mo.	Stationary	19 yr. 2 mo.
11	45	F	Squamous cell carcinoma of face			Plaque	660	Single	8 yr. 2 mo.	Stationary	25 yr. 4 mo.
12	34	M	Basal cell carcinoma of lid			Plaque	660	Single	4 yr. 7 mo.	Progressive	5 yr. 2 mo.
13	67	F	Basal cell carcinoma of nose			Plaque	660	Single	2 yr. 10 mo.	Progressive	4 yr. 2 mo.
14	68	M	Basal cell carcinoma of nose			Plaque	700	Single	8 yr. 7 mo.	Stationary	8 yr. 7 mo.
15	62	M	Basal cell carcinoma of cheek			Plaque	700	Single	2 yr. 11 mo.	Progressive	9 yr. 7 mo.
16	52	M	Basal cell carcinoma of lid			Plaque	750	Single	1 yr. 1 mo.	Indeterminate	3 yr. 11 mo.
17	64	M	Basal cell carcinoma of face			Plaque	800	Single	2 yr. 3 mo.	Progressive	12 yr. 2 mo.
18	53	M	Basal cell carcinoma of lid			Plaque	800	Single	4 yr. 1 mo.	Progressive	22 yr. 1 mo.
19	61	M	Basal cell carcinoma of face			Plaque	1,050	Single	2 yr. 11 mo.	Progressive	22 yr. 3 mo.
20	40	F	Squamous cell carcinoma of lid			Plaque	1,150	Single	5 yr. 5 mo.	Progressive	5 yr. 10 mo.

TABLE I—*Continued*

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time Cataract First Seen	Progressive or Stationary	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium					
TREATMENT TIME—3 WEEKS TO 3 MONTHS											
21	34	M	Carcinoma of ethmoid		370		400	2 mo.	2 yr. 5 mo.	Stationary	18 yr.
22	48	F	Basal cell carcinoma of cheek			Seeds 450	450	3 wk.	6 yr. 2 mo.	Stationary	10 yr. 3 mo.
23	50	F	Carcinoma of antrum		500		500	7 wk.	12 yr. 4 mo.	Stationary	14 yr. 6 mo.
24	40	M	Basal cell carcinoma of cheek			Seeds 530	530	2 mo.	4 yr. 2 mo.	Indeterminate	10 yr. 11 mo.
25	3 mo.	M	Retinoblastoma		560		560	3 mo.	1 yr. 7 mo.	Stationary	2 yr. 10 mo.
26	9 mo.	M	Retinoblastoma		560		560	2½ mo.	4 yr. 1 mo.	Stationary	4 yr. 1 mo.
27	9½ mo.	M	Retinoblastoma		560		560	2½ mo.	2 yr. 6 mo.	Progressive	3 yr 6 mo.
28	18	M	Aesthesioneuroblastoma of nose		60	Nasal Capsule 540	600	1 mo.	19 yr. 4 mo.	Stationary	19 yr. 7 mo.
29	76	F	Basal cell carcinoma of face			Seeds 600	600	3 wk.	4 yr. 7 mo.	Stationary	6 yr. 1 mo.
30	2 yr. 7 mo.	M	Retinoblastoma		650		650	3 mo.	2 yr. 3 mo.	Stationary	7 yr. 7 mo.
31	72	F	Basal cell carcinoma of face	800			800	2 mo.	1 yr. 2 mo.	Indeterminate	1 yr. 4 mo.
32	50	F	Basal cell carcinoma of face			Seeds 800	800	3 wk.	5 yr. 6 mo.	Stationary	9 yr. 9 mo.
33	1 yr. 8 mo.	F	Retinoblastoma		850		850	3 mo.	3 yr. 7 mo.	Stationary	7 yr. 7 mo.
34	1 yr. 2 mo.	M	Retinoblastoma		900		900	3 mo.	2 yr. 9 mo.	Stationary	11 yr. 11 mo.
35	4 mo.	M	Retinoblastoma		900		900	3 mo.	3 yr. 2 mo.	Progressive	3 yr. 10 mo.
36	4 yr.	M	Retinoblastoma		900		900	3 mo.	4 yr. 7 mo.	Progressive	9 yr. 1 mo.
37	6 mo.	F	Retinoblastoma		900		900	3 mo.	3 yr. 8 mo.	Stationary	6 yr. 10 mo.
38	1 yr. 6 mo.	M	Retinoblastoma		900		900	3 mo.	4 yr. 9 mo.	Indeterminate	5 yr. 8 mo.
39	8 mo.	F	Retinoblastoma		900		900	3 mo.	2 yr. 8 mo.	Progressive	6 yr. 4 mo.
40	2 yr. 6 mo.	M	Retinoblastoma		900		900	3 mo.	3 yr. 4 mo.	Stationary	4 yr. 6 mo.
41	1 yr. 3 mo.	F	Retinoblastoma		900		900	3 mo.	6 yr. 9 mo.	Stationary	6 yr. 9 mo.

TABLE I—*Continued*

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time Cataract First Seen	Progressive or Stationary	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium					
TREATMENT TIME—3 WEEKS TO 3 MONTHS											
42	2 yr.	F	Retinoblastoma		900		900	3 mo.	3 yr. 6 mo.	Stationary	12 yr. 4 mo.
43	8 mo.	F	Retinoblastoma		900		900	3 mo.	1 yr. 7 mo.	Progressive	11 yr. 9 mo.
44	2 yr. 3 mo.	M	Retinoblastoma		900		900	3 mo.	1 yr. 8 mo.	Progressive	9 yr. 9 mo.
45	3 mo.	M	Retinoblastoma		900		900	3 mo.	1 yr. 7 mo.	Progressive	2 yr. 4 mo.
46	67	M	Basal cell carcinoma of face			Seeds 950	950	3 wk.	3 yr.	Indeterminate	9 yr. 5 mo.
47	76	F	Basal cell carcinoma of face			Seeds 1,050	1,050	3 wk.	4 yr. 7 mo.	Progressive	6 yr. 1 mo.
48	1 yr.	M	Hemangioma of lid			Seeds 1,150	1,150	3 wk.	6 yr. 3 mo.	Stationary	10 yr. 5 mo.
49	56	M	Basal cell carcinoma of face			Seeds 1,400	1,400	3 wk.	6 yr. 6 mo.	Stationary	15 yr. 5 mo.
50	48	F	Basal cell carcinoma of cheek			Seeds 1,450	1,450	3 wk.	6 yr. 2 mo.	Progressive	10 yr. 3 mo.
51	64	M	Basal cell carcinoma of face			Seeds 1,700	1,700	3 wk.	4 yr. 9 mo.	Progressive	5 yr. 4 mo.
52	54	F	Basal cell carcinoma of face			Seeds 1,750	1,750	3 wk.	3 mo.	Progressive	17 yr.
53	63	F	Basal cell carcinoma of face			Seeds 1,800	1,800	3 wk.	3 yr. 3 mo.	Progressive	4 yr. 4 mo.
54	51	M	Squamous cell carcinoma of conjunctiva			Plaque 1,850	1,850	4 wk.	11 yr. 11 mo.	Stationary	28 yr. 6 mo.
55	64	F	Basal cell carcinoma of face			Seeds 2,000	2,000	3 wk.	6 yr. 7 mo.	Progressive	12 yr.
56	75	M	Basal cell carcinoma of face			Seeds 2,000	2,000	3 wk.	1 yr. 4 mo.	Progressive	1 yr. 9 mo.
57	55	F	Basal cell carcinoma of face			Seeds 2,350	2,350	3 wk.	5 yr. 5 mo.	Indeterminate	8 yr. 8 mo.
58	40	M	Basal cell carcinoma of face			Seeds 2,400	2,400	3 wk.	2 yr. 8 mo.	Progressive	9 yr. 5 mo.
59	64	M	Basal cell carcinoma of face			Seeds 2,400	2,400	3 wk.	3 yr. 2 mo.	Progressive	4 yr. 1 mo.
60	46	M	Carcinoma of nasopharynx		2,800		2,800	3 wk.	3 yr. 2 mo.	Progressive	19 yr.
61	50	M	Basal cell carcinoma of face	50		Seeds 2,950	3,000	3 wk.	2 yr.	Progressive	2 yr. 3 mo.
62	84	F	Carcinoma of nasal cavity		1,050	Nasal Capsule 2,200	3,250	2 mo.	2 yr. 6 mo.	Progressive	4 yr. 4 mo.

TABLE I—*Continued*

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time Cataract First Seen	Progressive or Stationary	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium					
TREATMENT TIME—3 WEEKS TO 3 MONTHS											
63	50	F	Basal cell carcinoma of face			Seeds 3,300	3,300	3 wk.	3 yr. 4 mo.	Progressive	20 yr. 6 mo.
64	12	F	Carcinoma of ethmoid		3,900		3,900	1 mo.	1 yr. 6 mo.	Progressive	4 yr. 8 mo.
65	41	M	Basal cell carcinoma of face			Seeds 4,000	4,000	3 wk.	2 yr. 6 mo.	Progressive	20 yr.
66	34	M	Carcinoma of ethmoid		6,000		6,000	2 mo.	4 mo.	Progressive	17 yr. 9 mo.
67	69	M	Basal cell carcinoma of face			Seeds 6,100	6,100	3 wk.	2 yr. 6 mo.	Progressive	15 yr. 5 mo.
68	12	M	Fibroma of nasopharynx			Seeds Over 1,500	Over 1,500	1 mo.	4 yr. 1 mo.	Progressive	19 yr. 9 mo.
69	50	F	Carcinoma of antrum			Seeds Radium Pack	Over 1,500	1 mo.	3 yr.	Progressive	19 yr. 1 mo.
TREATMENT TIME—OVER 3 MONTHS											
70	62	M	Basal cell carcinoma of face			Plaque Seeds	550	5 mo.	3 yr. 8 mo.	Progressive	4 yr. 4 mo.
71	9½ mo.	F	Retinoblastoma		550		550	1 yr. 3 mo.	4 yr.	Stationary	20 yr. 5 mo.
72	70	F	Basal cell carcinoma of face			Plaque Seeds Bulb	750	2 yr. 9 mo.	3 yr. 10 mo.	Progressive	7 yr. 4 mo.
73	6	F	Osteogenic sarcoma of maxilla			Seeds 800	800	11 mo.	24 yr. 6 mo.	Stationary	25 yr. 5 mo.
74	1 yr 2 mo.	F	Retinoblastoma		900		900	5 mo.	3 yr. 10 mo.	Stationary	6 yr. 2 mo.
75	1½ mo.	M	Hemangioma of cheek			Plaque Seeds	1,100	7 mo.	5 yr. 10 mo.	Stationary	9 yr. 2 mo.
76	6	F	Osteogenic sarcoma of maxilla			Seeds 1,200	1,200	11 mo.	10 yr. 8 mo.	Stationary	25 yr. 5 mo.
77	2 mo.	F	Hemangioma of cheek			Tray Plaque Seeds	1,250	1 yr.	2 yr. 9 mo.	Progressive	9 yr.
78	59	M	Basal cell carcinoma of face			Tray Plaque Silver Tubes	1,350	3 yr. 10 mo.	8 yr. 6 mo.	Indeterminate	13 yr. 10 mo.
79	68	F	Carcinoma of antrum		100	Seeds 1,400	1,500	3 mo. 3 wk.	4 yr. 8 mo.	Stationary	5 yr. 1 mo.
80	63	F	Squamous cell carcinoma of nose			Plaque	1,550	9 yr.	1 yr. 2 mo.	Progressive	17 yr. 3 mo.
81	40	F	Meningioma of optic nerve			Tray	1,700	8 mo.	5 yr. 6 mo.	Progressive	15 yr. 2 mo.

TABLE I—*Continued*

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time Cataract First Seen	Progressive or Stationary	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium					
TREATMENT TIME—OVER 3 MONTHS											
82	4	F	Lymphangioma of lid			Plaque Seeds	1,700	8 yr. 3 mo.	7 yr. 3 mo.	Stationary	19 yr.
83	75	M	Basal cell carcinoma of face			Plaque Seeds	2,050	2 yr.	3 yr. 3 mo.	Progressive	5 yr.
84	4 wk.	F	Hemangioma of face			Plaque Seeds	2,150	4 mo.	17 yr. 9 mo.	Stationary	18 yr. 1 mo.
85	11 mo.	M	Retinoblastoma		2,150		2,150	9 mo.	1 yr.	Progressive	8 yr. 11 mo.
86	44	F	Squamous cell carcinoma of nose			Plaque Tray Seed	2,300	6 yr.	5 yr. 4 mo.	Progressive	20 yr. 6 mo.
87	5½	M	Retinoblastoma		2,700		2,700	1 yr. 7 mo.	1 yr. 9 mo.	Progressive	6 yr. 6 mo.
88	14 mo.	F	Retinoblastoma		2,700		2,700	1 yr. 2 mo.	6 mo.	Progressive	16 yr. 9 mo.
89	77	M	Basal cell carcinoma of face	100	2,000	Seeds 2,700	4,800	1 yr.	2 yr. 6 mo.	Progressive	5 yr. 5 mo.
90	52	F	Squamous cell carcinoma of lid			Plaque Seeds	5,300	8 yr. 7 mo.	2 yr. 4 mo.	Progressive	17 yr. 5 mo.
91	9	F	Retinoblastoma		6,900		6,900	2 yr. 3 mo.	1 yr.	Progressive	4 yr. 10 mo.
92	59	F	Schneiderian carcinoma of antrum			Radium Pack Monel Ball Seeds	Over 1,500	1 yr. 4 mo.	6 yr. 9 mo.	Progressive	12 yr. 4 mo.
93	21	M	Melanoma of orbit			Tray Radium Pack	Over 1,500	1 yr. 1 mo.	1 yr. 3 mo.	Progressive	30 yr. 11 mo.
94	3 mo.	F	Hemangioma of face			Tray Seeds	Over 1,500	1 yr. 6 mo.	3 yr. 2 mo.	Progressive	14 yr. 9 mo.
95	62	M	Basal cell carcinoma of face			Plaque Seeds	Over 1,500	5 mo.	3 yr. 8 mo.	Progressive	4 yr. 4 mo.
96	83	F	Basal cell carcinoma of face			Plaque Seeds	Over 1,500	1 yr. 4 mo.	3 yr. 7 mo.	Progressive	6 yr. 11 mo.
97	58	F	Basal cell carcinoma of face			Seeds Bulb	Over 1,500	3 yr.	4 yr. 2 mo.	Progressive	5 yr.
98	1	F	Hemangioma of face		650		650	2 da.	2 yr. 5 mo.	Stationary	3 yr. 6 mo.
99	64	M	Basal cell carcinoma of nose			Plaque	1,950	10 da.	2 yr. 9 mo.	Progressive	2 yr. 9 mo.
100	62	M	Basal cell carcinoma of face	1,150	2,600		3,750	2 wk.	8 mo.	Progressive	3 yr. 8 mo.

TABLE II

NON-CATARACTS

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time of Last Eye Examination after Treatment	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium				
SINGLE TREATMENT										
1	64	M	Basal cell carcinoma of lid			Plaque	40	Single	3 yr. 10 mo.	12 yr. 2 mo.
2	74	M	Basal cell carcinoma of lid			Bulb	45	Single	6 yr. 3 mo.	8 yr. 4 mo.
3	58	F	Basal cell carcinoma of face	50			50	Single	3 yr. 5 mo.	8 yr. 5 mo.
4	45	F	Basal cell carcinoma of forehead			Plaque	60	Single	8 yr. 10 mo.	16 yr. 2 mo.
5	78	F	Basal cell carcinoma of face	45		Seeds 20	65	Single	5 yr. 10 mo.	5 yr. 10 mo.
6	55	F	Basal cell carcinoma of nose			Plaque	75	Single	17 yr.	17 yr.
7	74	M	Basal cell carcinoma of lid			Bulb	75	Single	6 yr. 3 mo.	8 yr. 4 mo.
8	43	F	Basal cell carcinoma of lid	85			85	Single	3 yr. 2 mo.	11 yr. 3 mo.
9	64	F	Basal cell carcinoma of face			Plaque Bulb	95	Single	4 yr. 10 mo.	13 yr. 9 mo.
10	63	M	Basal cell carcinoma of lid			Plaque	125	Single	9 yr. 10 mo.	15 yr. 10 mo.
11	61	M	Basal cell carcinoma of nose			Plaque	130	Single	16 yr. 4 mo.	22 yr. 3 mo.
12	40	F	Basal cell carcinoma of lid			Plaque	150	Single	5 yr. 10 mo.	5 yr. 10 mo.
13	63	M	Basal cell carcinoma of nose			Plaque	160	Single	8 yr. 7 mo.	8 yr. 7 mo.
14	67	F	Basal cell carcinoma of nose			Plaque	160	Single	4 yr. 2 mo.	4 yr. 2 mo.
15	34	M	Basal cell carcinoma of lid			Plaque	165	Single	5 yr. 2 mo.	5 yr. 2 mo.
16	45	F	Squamous cell carcinoma of face			Plaque	165	Single	8 yr. 9 mo.	25 yr. 5 mo.
17	68	M	Basal cell carcinoma of face			Plaque	175	Single	8 yr. 7 mo.	8 yr. 7 mo.
TREATMENT TIME—3 WEEKS TO 3 MONTHS										
18	51	M	Basal cell carcinoma of lid			Seeds 40	40	3 wk.	28 yr. 6 mo.	28 yr. 6 mo.
19	52	F	Keratosis of lid			Seeds 60	60	3 wk.	5 yr. 1 mo.	8 yr. 2 mo.
20	50	F	Basal cell carcinoma of lid			Seeds 80	80	3 wk.	9 yr. 9 mo.	10 yr. 3 mo.

TABLE II—*Continued*

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time of Last Eye Examination after Treatment	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium				
TREATMENT TIME—3 WEEKS TO 3 MONTHS										
21	70	M	Carcinoma of mucosa of cheek		30	Seeds 60	90	1 mo. 2 wk.	8 yr.	9 yr.
22	41	M	Basal cell carcinoma of lid			Seeds 120	120	3 wk.	20 yr. 7 mo.	20 yr. 7 mo.
23	55	F	Basal cell carcinoma of lid			Seeds 120	120	3 wk.	5 yr. 5 mo.	8 yr. 8 mo.
24	67	M	Basal cell carcinoma of face			Seeds 130	130	3 wk.	4 yr. 7 mo.	9 yr. 5 mo.
25	40	M	Basal cell carcinoma of lid			Seeds 140	140	3 wk.	19 yr. 1 mo.	19 yr 1 mo.
26	50	F	Carcinoma of antrum		150		150	1 mo. 1 wk.	14 yr. 3 mo.	14 yr. 5 mo.
27	69	M	Basal cell carcinoma of lid			Seeds 175	175	3 wk.	6 yr. 4 mo.	15 yr. 5 mo.
28	50	F	Basal cell carcinoma of lid			Seeds 200	200	3 wk.	16 yr. 9 mo.	20 yr. 5 mo.
29	40	M	Basal cell carcinoma of face			Seeds 200	200	2 mo.	4 yr. 2 mo.	10 yr. 1 mo.
30	63	F	Basal cell carcinoma of lid			Seeds 200	200	3 wk.	3 yr. 10 mo.	4 yr. 4 mo.
31	54	F	Basal cell carcinoma of lid			Seeds 250	250	3 wk.	10 yr. 9 mo.	17 yr.
32	56	M	Basal cell carcinoma of lid			Seeds 250	250	3 wk.	13 yr. 11 mo.	13 yr. 11 mo.
33	64	M	Basal cell carcinoma of lid			Seeds 300	300	3 wk.	3 yr. 2 mo.	4 yr. 1 mo.
34	53	M	Lymphosarcoma of nasal cavity		300		300	1 mo. 1 wk.	13 yr. 7 mo.	13 yr. 7 mo.
35	54	M	Basal cell carcinoma of cheek	30		300	330	3 wk.	3 yr. 3 mo.	4 yr. 2 mo.
36	72	M	Carcinoma of mucosa of cheek		80	Seeds 280	360	1 mo.	7 yr.	11 yr. 8 mo.
37	53	M	Squamous cell carcinoma of face	100		300	400	3 wk.	15 yr. 5 mo.	15 yr. 5 mo.
38	48	F	Lymphosarcoma of antrum		450		450	1 mo.	4 yr. 2 mo.	4 yr. 4 mo.
39	52	F	Keratosis of lid			Seeds 500	500	3 wk.	5 yr. 1 mo.	8 yr. 2 mo.
40	18	F	Aesthesioneuroblastoma of nose		50	450	500	2 mo.	19 yr. 5 mo.	19 yr. 7 mo.
41	2 mo.	M	Retinoblastoma		560		560	2 mo. 3 wk.	5 yr. 9 mo.	5 yr. 9 mo.

TABLE II—*Continued*

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time of Last Eye Examination after Treatment	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium				
TREATMENT TIME—3 WEEKS TO 3 MONTHS										
42	2	F	Retinoblastoma		650		650	3 mo.	6 yr. 6 mo.	6 yr. 6 mo.
43	1	M	Retinoblastoma		650		650	3 mo.	6 yr. 9 mo.	6 yr. 9 mo.
44	46	M	Carcinoma of nasopharynx		700		700	3 wk.	17 yr. 3 mo.	19 yr.
45	4	F	Retinoblastoma		850		850	2 mo. 3 wk.	10 yr.	10 yr.
46	10 mo.	M	Retinoblastoma		900		900	3 mo.	9 yr. 7 mo.	9 yr. 7 mo.
47	10 mo.	M	Retinoblastoma		900		900	3 mo.	9 yr. 8 mo.	9 yr. 8 mo.
48	3	F	Retinoblastoma		900		900	3 mo.	3 yr. 7 mo.	3 yr. 7 mo.
49	2	M	Retinoblastoma		900		900	3 mo.	3 yr. 4 mo.	3 yr. 4 mo.
50	1 yr. 5 mo.	M	Retinoblastoma		900		900	2 mo. 3 wk.	5 yr. 10 mo.	5 yr. 10 mo.
51	1 yr. 9 mo.	F	Retinoblastoma		900		900	2 mo. 3 wk.	3 yr. 6 mo.	3 yr. 6 mo.
52	1	F	Retinoblastoma		900		900	3 mo.	3 yr. 9 mo.	3 yr. 9 mo.
53	5	M	Retinoblastoma		900		900	1 mo. 3 wk.	15 yr. 7 mo.	15 yr. 7 mo.
54	58	F	Carcinoma of antrum			Monel Bulb + Seeds	900	1 mo.	5 yr. 1 mo.	8 yr.
55	3 mo.	M	Retinoblastoma		850	150	1,000	2 mo. 2 wk.	12 yr. 9 mo.	13 yr. 8 mo.
TREATMENT TIME—OVER 3 MONTHS										
56	4 wk.	F	Hemangioma of face			Plaque Seeds	120	4 mo.	17 yr. 9 mo.	18 yr. 1 mo.
57	75	M	Basal cell carcinoma of lid			Plaque Seeds	130	2 yr. 3 mo.	3 yr. 11 mo.	5 yr.
58	6 wk.	M	Hemangioma of cheek			Plaque Seeds	180	7 mo.	8 yr. 7 mo.	9 yr. 2 mo.
59	47	M	Carcinoma of palate			Seeds 310	310	3 yr. 4 mo.	3 yr. 1 mo.	3 yr. 6 mo.
60	59	M	Melanoma of face			Tray Plaque	330	1 yr. 5 mo.	11 yr. 5 mo.	13 yr. 10 mo.
61	83	F	Basal cell carcinoma of face			Plaque Seeds	400	1 yr. 6 mo.	4 yr. 3 mo.	7 yr.

TABLE II—*Continued*

Case No.	Age	Sex	Diagnosis	Method of Treatment			Dose in r to Lens	Duration Treatment	Time of Last Eye Examination after Treatment	Length of Follow-up
				100–140 kv.	200–250 kv.	Radium				
TREATMENT TIME—OVER 3 MONTHS										
62	52	F	Squamous cell carcinoma of lid			Plaque Seeds	500	8 yr. 7 mo.	5 yr. 7 mo.	8 yr. 10 mo.
63	40	F	Meningioma of optic nerve			Tray	500	8 mo.	14 yr. 6 mo.	14 yr. 6 mo.
64	9 wk.	F	Hemangioma of face			Tray Seeds Plaque	530	1 yr.	9 yr. 6 mo.	20 yr. 1 mo.
65	4	F	Lymphangioma of lids and orbit			Seeds Plaque	550	8 yr. 3 mo.	20 yr. 9 mo.	20 yr. 9 mo.
66	77	M	Basal cell carcinoma of nose			Seeds 550	550	3 yr. 2 mo.	4 yr. 1 mo.	5 yr. 6 mo.
67	47	M	Carcinoma of palate		150	700	850	3 yr. 4 mo.	3 yr. 1 mo.	3 yr. 6 mo.
68	1 yr. 3 mo.	F	Retinoblastoma		900		900	3 mo. 3 wk.	8 yr. 8 mo.	8 yr. 8 mo.
69	44	F	Squamous cell carcinoma of nose			Seeds 950	950	6 yr.	12 yr. 9 mo.	20 yr. 6 mo.
70	3 mo.	F	Hemangioma of face			Tray Seeds	1,100	1 yr. 6 mo.	22 yr.	22 yr.
71	48	F	Basal cell carcinoma of face	25			25	1 wk.	3 yr. 8 mo.	11 yr. 8 mo.
72	68	M	Basal cell carcinoma of face	80			80	2½ wk.	6 yr. 11 mo.	6 yr. 11 mo.
73	62	M	Basal cell carcinoma of face		80		80	2 wk.	3 yr. 8 mo.	3 yr. 8 mo.

treatment alone was at least 1,500 r at the lens. In the other instances, all of which had progressive cataracts, and where only a few of the multiple treatments resulted in a dose of 1500 r, an attempt to estimate the total dose was not considered necessary.

METHOD OF MEASUREMENT

A phantom (Figure 1) was devised employing a skull of average size covered with a mixture of paraffin and beeswax (equal parts by weight) having unit density. The skull was coated in such a manner and thickness as to simulate normal skin and subcutaneous tissue and thus approximate the same amount of scatter to the eye from these structures. The cranial cavity was filled with bolus.* Plastic eyes (Figure 2) of approximately unit density were constructed. A hole was drilled in one side so that a small Baldwin-Farmer condenser ionization chamber[11] with a measuring volume 6 mm. long and 5 mm. in diameter could be inserted into the position of the lens and thus measure the amount of direct and scattered radiation to this structure. The eye is hollow and can be filled

* This is a composition of sucrose and magnesium carbonate in the form of small, hard spheres with an average diameter of about 2.3 mm. The electron density and effective atomic number are well within 1 per cent of the values for water. It has been tested for transmission for qualities ranging from 45 kv. through 90 kv., 220 kv., a million volts and gamma rays from radium, and no appreciable variation from the results with water have been detected at any quality. (Information supplied by the Lincolnshire Radiotherapy Center, War Memorial Hospital, Scunthorpe, England.)

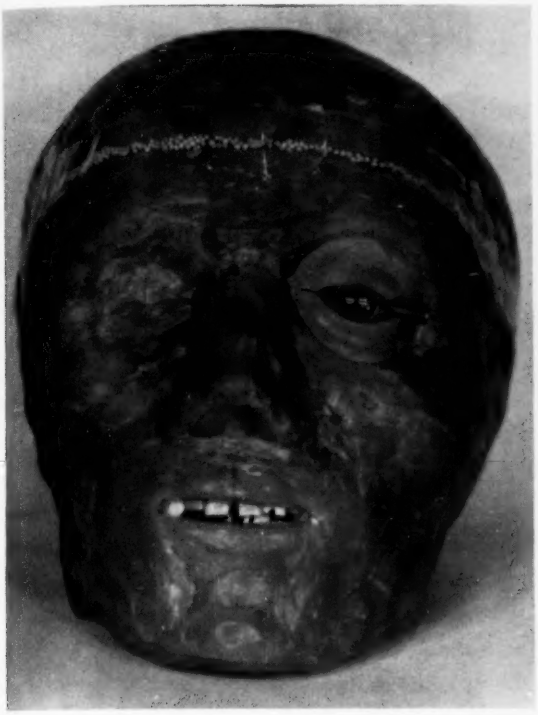

Fig. 1. Phantom skull used for measuring dose of radiation to the lens. Wax eyelids and plastic eye with ionization chamber in position of lens can be seen. Apex of orbit filled with wax, as seen on right, to maintain eye in proper position. Bolus used to fill calvarium seen above.

with bolus. The apices of the orbits of the phantom were filled with wax so that the eyes were in their normal positions. Lids, also of wax, were made, and at the lateral canthi a portion was cut away to allow the chamber to be inserted and removed.

The phantom was treated as was the patient for all the various types of lesions included in the series. The types of lesions for which measurements were taken include hemangiomas of the lids, orbit, cheek and mouth, and various types of carcinomas of the lids, eye, nose, nasopharynx, sinuses, cheek, palate and gum. Oral treatments were reduplicated on the phantom when indicated (Figure 3). In each case the factors, shielding and positioning were reduplicated as closely as possible from the data available in the chart which usually included diagrams or photographs. In some cases, particularly for the

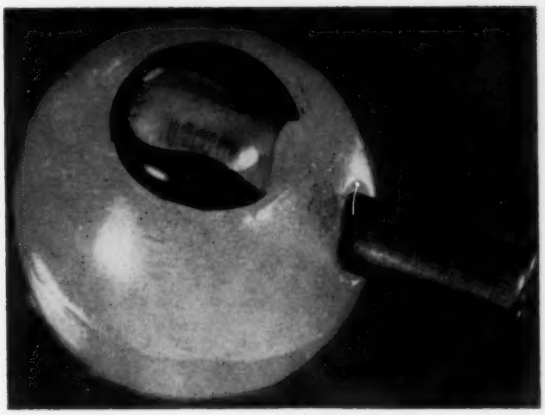

Fig. 2. Plastic eye used for measuring dose to lens shown with ionization chamber inserted through hole in side into position of the lens.

group of retinoblastomas, the positioning was checked by taking roentgenograms with the therapy machine using lead markers placed at the estimated site of the

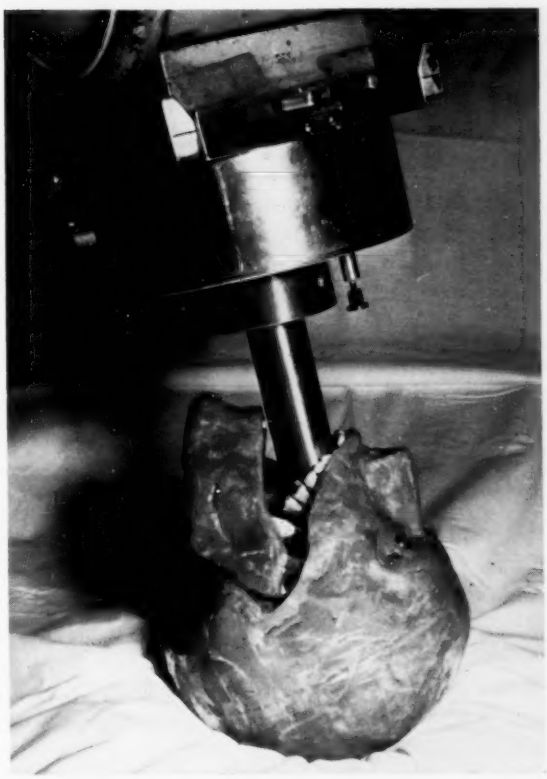

Fig. 3. Phantom in position for peroral treatment such as was used for carcinoma of hard palate or nasopharynx. Ionization chamber can be seen in position to measure scattered radiation.

FIG. 4. One of original masks used in treatment of a carcinoma of the antrum and nose, shown in position on the phantom.

lesion. The original shields or duplicates were employed. Every measurement was rechecked several times. Many of the radium cases were cross-checked by measuring with calipers the distance from the radium or seeds to the lens on the phantom. The dose was then calculated on the basis of 8.4 r per milligram hour at 1 cm. and the inverse square law. When shields were used, an allowance was made for the small amount of lead absorption. In most instances measurements were made to both eyes. Some of the types of setups and shields are shown in Figures 4, 5, 6, and 7.

It is appreciated that in attempting to reduplicate therapy, there are numerous uncontrollable variables. Among such factors are variations in the size and shape of skulls, the thickness of the tissues, the interorbital distance, the configuration of the nose, movement by the patient, and the shielding of the roentgen ray tubes. It is for this reason that intervals of 200 r have been chosen, as will be seen, in tabulating the dose to the lens.

The voltages employed ranged from 100–250 kv. with a half-value layer of 1.0 mm. Al to 2 mm. Cu. The chambers were calibrated for the quality of radiation used and frequent checks made for leakage. The chambers were read in a Baldwin-Farmer electrometer.

When radium plaques were employed, the original plaques, loaded in a similar manner, were taped or strapped to the phantom. Every effort was made to reduplicate the positioning of the plaques. In most instances photographs of the original lesion were available which greatly aided in the proper placing of the plaques.

When gold seeds were used, these were distributed in a piece of cork the same size as the area treated and taped to the proper area on the phantom. If treatment had been by a nasopharyngeal applicator this was inserted into the phantom in approximately the same position it had been on the patient. The ionization chambers were

FIG. 5. Phantom in position for treatment using lead mask shown in Figure 4. The eye is in the direct beam, although shielded by 2.0 mm. lead.

calibrated for radium whenever it was used.

The roentgen ray and radium doses have been grouped in this study and are all reported as roentgens at the lens. This was done primarily because much of the radium was implanted at some distance from the eyes, and therefore the quality of the radiation was decreased somewhat by scattering before reaching the lens. Also, a relative biologic effect of the two is known fairly definitely only for a skin threshold erythema.[12] Moreover, the dosage intervals taken in plotting the findings in Figure 9 are rather wide (200 r intervals) which would largely mask any relative biologic effect. In the recent experimental work of Upton and his group[31] on mice, a relative biologic effect for severe lens opacities of 1.2 to 1.3 was found with roentgen rays of half-value layer 0.55 mm. Cu compared to Co^{60} gamma rays taken as 1. A similar ratio was found for roentgen rays of half-value layer 1.93 mm. Cu as compared to gamma rays from a nuclear detonation. This is within the 200 r limits used in Figure 9 before the 100 per cent incidence is reached. This figure includes all degrees of opacities. In the other tables the dosage intervals are even greater.

FIG. 6. Phantom in position for treatment of carcinoma of antrum through an anterior port. The eye is at the edge of the beam and is not shielded. Dose to both eyes measured.

FIG. 7. Phantom in same position as shown in Figure 6 but with 2.0 mm. Pb shield protecting the eye. Dose to both eyes measured.

RESULTS

1. *Dose to Lens Which Produced Cataract*

In general, for a given quality of radiation and duration of treatment, it would be expected that because of individual variations of the patients there would be a threshold or minimum dose at which a small percentage of the lenses would show a certain degree of opacity. As the dose increased a larger and larger percentage of the patients would be expected to show lens changes until, at a large enough dose, 100 per cent of the lenses should develop cataracts.

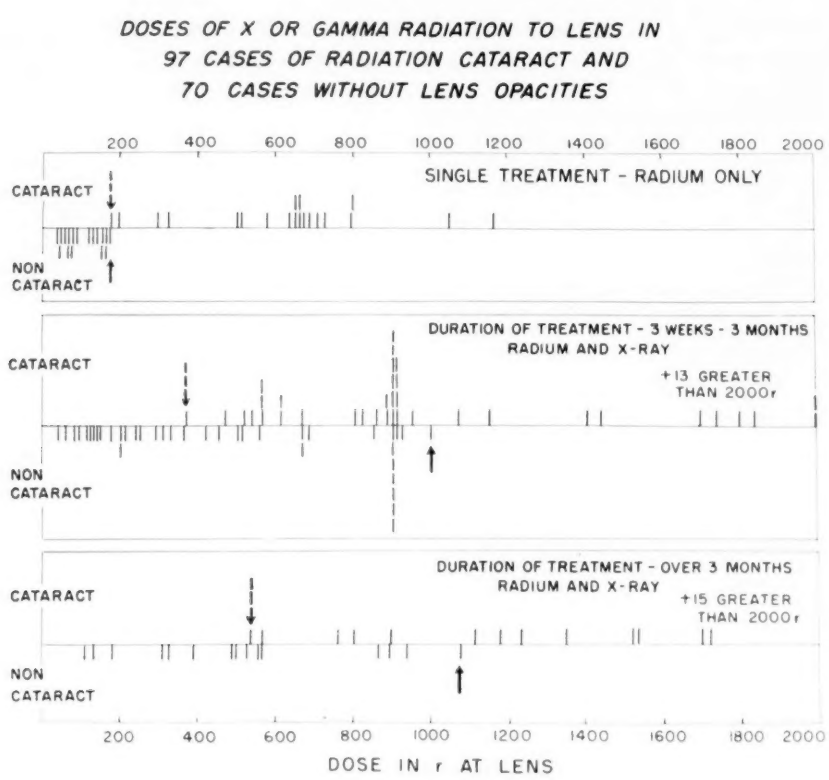
DOSES OF X OR GAMMA RADIATION TO LENS IN
97 CASES OF RADIATION CATARACT AND
70 CASES WITHOUT LENS OPACITIES
200 400 600 800 1000 1200 1400 1600 1800 2000
SINGLE TREATMENT - RADIUM ONLY
CATARACT
NON CATARACT
DURATION OF TREATMENT - 3 WEEKS - 3 MONTHS
RADIUM AND X-RAY
+13 GREATER THAN 2000r
CATARACT
NON CATARACT
DURATION OF TREATMENT - OVER 3 MONTHS
RADIUM AND X-RAY
+15 GREATER THAN 2000r
CATARACT
NON CATARACT
200 400 600 800 1000 1200 1400 1600 1800 2000
DOSE IN r AT LENS

FIG. 8

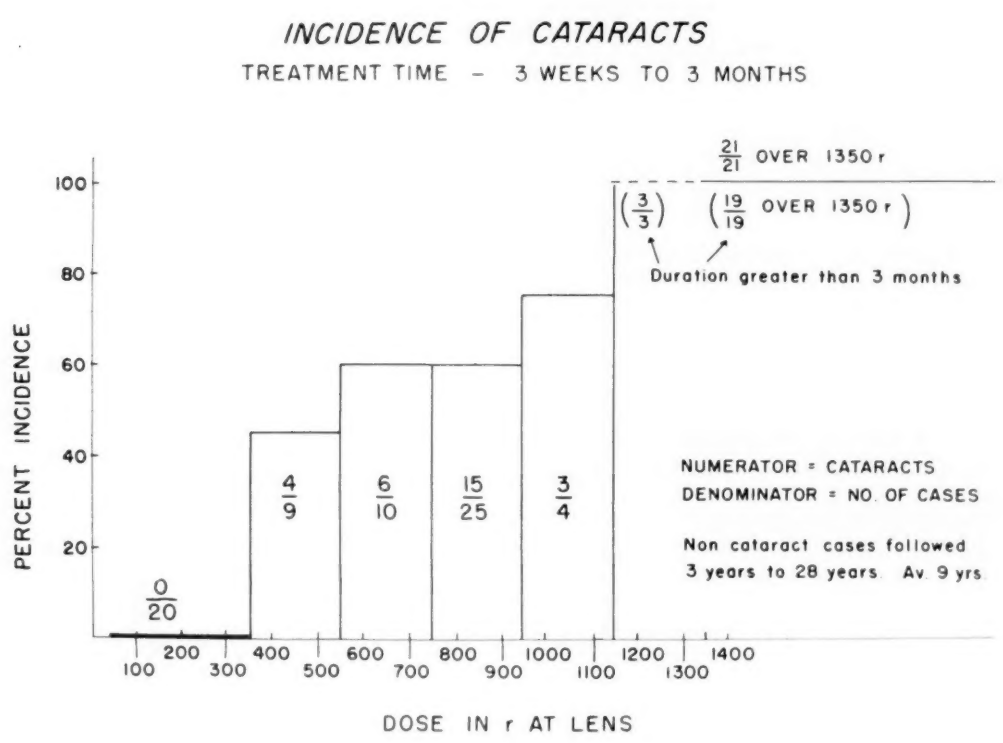
INCIDENCE OF CATARACTS
TREATMENT TIME - 3 WEEKS TO 3 MONTHS
21/21 OVER 1350 r
(3/3) (19/19 OVER 1350 r)
Duration greater than 3 months
PERCENT INCIDENCE
100
80
60
40
20
0/20
4/9
6/10
15/25
3/4
NUMERATOR = CATARACTS
DENOMINATOR = NO. OF CASES
Non cataract cases followed
3 years to 28 years. Av. 9 yrs
100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400
DOSE IN r AT LENS

FIG. 9

In an uncontrolled series such as this, it is impossible to determine accurately the absolute threshold. The minimum doses given below thus represent the smallest amount of roentgen or gamma radiation that produced any degree of opacity in the cases studied.

It is also impossible to classify the cases according to dose and degree of lens opacities, such as can be done in large numbers of controlled experimental studies with animals. Many of the persons reported here are dead, and numerous others have refused to return for examination. Repeated efforts were made to contact all the living patients and re-examine their eyes, but the response was not sufficient to permit a correlation of dose and degree of opacity. The most that can be done, as will be discussed below, is to classify the cataracts according to whether the opacities were stationary or progressive and attempt to relate this to dose.

For the entire group of 100 cases of radiation cataracts, the dosage range was from 200 r to 6,900 r at the lens. This included single and multiple treatments and a wide range of duration of therapy. For more accurate analysis the group has been subdivided into single treatments, multiple or divided treatments from 3 weeks to 3 months, and divided treatments over a period greater than 3 months. The results for 97 cataract cases and 70 non-cataract cases are shown in Figure 8. Three cases with lens opacities were omitted from Figure 8 since their treatment times were 2 days, 10 days, and 2 weeks. These did not fit into any of the three categories shown. The dose to the lens in these cases was 650 r, 1,950 r, and 3,750 r, respectively. Three non-cataract cases were also excluded since they had treatment times of 1, 2 and 2½ weeks. Their doses were 80 r, 80 r and 25 r. All doses are given in r to the lens. Each line above the horizontal line represents a cataract and those below are non-cataracts. Individual cases are not shown separately for doses over 2,000 r.

(a) *Single Treatments.* There were 37 cases which received their irradiation in a single treatment and 20 of these developed lens opacities. The other 17 patients received doses from 40 r to 175 r to the lens without developing lens changes. Above this dose, from 200 r to 1,150 r, all the cases developed cataracts attributable to irradiation. The fifty-three year old patient with the lens opacity that resulted from the minimum dose of 200 r had his first eye examination 22 years, 1 month after treatment. The cataract was stationary.

It is interesting that all of these patients were treated with radium plaques. This does not *per se* indicate a greater sensitivity of the lens to gamma radiation but simply means that there were no single exposures to roentgen radiation in this group.

(b) *Multiple Treatments (3 weeks to 3 months).* A total of 87 cases in this group was measured, and of these 49 developed radiation cataracts with doses to the lens from 400 r to 6,100 r of roentgen and gamma radiation, delivered in 3 weeks to 3 months. Of the four lowest doses in this group, 2 cataracts resulted from roentgen rays and 2 from radium. The lens opacity with the dose of 400 r was first seen 2 years, 5 months after treatment and the cataract was stationary. The duration of the treatment with radium seeds has been taken as 3 weeks. At this time about 97 per cent of the total radiation had been given. These 87 cases included adults and children. The latter will be discussed separately elsewhere.

(c) *Divided Dose (over 3 months).* There were 43 cases in this group of which 28 developed cataracts with doses to the lens ranging from 550 r to 6,900 r. The lens opacity with the dose of 550 r was first seen 3 years, 8 months after treatment and the cataract was progressive.

A comparison of the lowest dose at which the lens changes began to appear in each group is interesting. For the single treatment group the lowest cataractogenic dose found was 200 r, for the group with the divided doses of 3 weeks to 3 months, it was 400 r, and for the group with greater

fractionation it was 550 r. This is indicated by the arrows above the lines on Figure 8. These figures suggest that the threshold dose increases with the duration of treatment.

It should be emphasized that in the single treatment group the fact that there were no cases without cataracts above 200 r probably does not mean that the lens cannot tolerate higher doses administered in a single treatment. Rather, because of the smaller number of cases (4) with doses to the lens in the range of 200 r to 500 r no non-cataract cases were found. Further studies at these dosage levels are necessary to determine more exactly the upper limit of tolerance.

The same qualifications apply to the group with a treatment time in excess of 3 months. However, the number of cases in the group with a treatment time of 3 weeks to 3 months was the largest, and, therefore, the results would be more accurate. This is the length of time in which most treatment is given which accounts for the larger size of the group. By the same token it also makes this information the most applicable clinically.

In these same three categories the highest dose at the lens that did not produce lens opacities is of some significance. These points are indicated by the arrows below the lines on Figure 8. In the single treatment group the maximum non-cataractogenic dose was 175 r in a patient followed 8 years, 7 months. In the group whose treatment was fractionated from 3 weeks to 3 months, the largest dose found without lens change was 1,000 r. The treatment time was 2 months, 2 weeks and the patient was followed 13 years, 8 months. Where the fractionation of therapy was greater than 3 months, the maximum dose without a cataract was 1,100 r. In this case the treatment time extended over 1 year, 6 months and the patient was followed 22 years. This seems to indicate that as the duration of treatment is prolonged the dose at which there is 100 per cent incidence of cataracts also increases.

2. *Incidence of Cataracts at Various Dosage Intervals*

In order to determine the incidence of lens opacities at various dosage intervals, a group of patients who had received measurable amounts of radiation to the eye with a similar duration of treatment was studied. For each dosage interval the number of cataracts was compared to the number of non-cataracts.

The results are shown in Figure 9 for a group of 111 patients. This includes 49 cataracts and 40 non-cataracts with a treatment time of 3 weeks to 3 months, and 22 cataracts with a treatment time of over 3 months. The cases are tabulated at 200 r intervals for the reasons previously given. The single treatment group is not shown since it has been discussed above. Also excluded are the 3 cataract cases with treatment times of 2 days, 10 days and 2 weeks, and 3 non-cataract cases with fractionated treatment times of less than 3 weeks.

Only 1 of the entire series showed a significant amount of radiation to the lens from 100–140 kv. roentgen rays and this was due to inadequate shielding. This quality of radiation, therefore, does not contribute significantly to that part of the histogram showing a positive incidence of cataracts. The injury to the lenses resulted from treatment with 200–250 kv. roentgen rays and radium.

In the group with a treatment time of 3 weeks to 3 months, there were no cases in the dosage range from 1,150 r to 1,350 r. However, there were 3 cases, all of which had cataracts, in this range in the group with a treatment time greater than 3 months. If the group with the longer treatment time reaches 100 per cent incidence at 1,150 r, it can be assumed that the cases with a shorter treatment time would also be at this 100 per cent level. Furthermore, all 43 cases over 1,150 r, irrespective of duration of treatment, developed lens opacities. Therefore, in order to complete the histogram the cases with doses to the

lens over 1,150 r with a treatment time of over 3 months are shown in Figure 9.

It is apparent in Figure 9 that in the group of cases with a treatment time of 3 weeks to 3 months no cataracts were observed in the 20 patients whose lenses received from 40 r to 350 r. In the range from 350 r to 550 r, 4 of 9 developed lens opacities. The minimum dose in this range was 400 r. From 550 r to 750 r, 6 of 10 patients developed lens changes. From 750 r to 950 r, 15 of 25 patients had cataracts and from 950 r to 1,150 r, 3 of 4 developed opacities.

In the group of cases in which divided treatments were given over a period greater than 3 months, there were 5 patients whose lenses received less than 350 r and in whom cataracts did not develop. In the same dosage range from 350 r to 550 r, 1 of 4 patients developed a lens opacity. The dose for this case was 550 r. In the range from 550 r to 750 r, 2 of 4 cases developed cataracts; from 750 r to 950 r, 3 of 5; from 950 r to 1,150 r, 1 of 2 and above this the incidence was 100 per cent. The number of cases is small in each dosage range and for this reason the cases with less than 1,150 r at the longer duration have not been shown on the histogram. However, as would be expected, the group with a treatment time over 3 months showed a lower incidence of cataracts for a given dose than the group with the treatment time of 3 weeks to 3 months.

The single treatment group showed a 100 per cent incidence above 200 r. The 100 per cent incidence for the group with a treatment time of 3 weeks to 3 months falls between the incidence of the shorter and longer times, as would be expected.

In view of the small number of cases, in each step of the histogram in Figure 9 percentages have been avoided. Further studies are necessary to define more exactly the per cent incidence of cataracts, particularly at the dosage levels of 350 r to 550 r, 550 r to 750 r and 950 r to 1,150 r. Nevertheless, the cases reported here give an indication of the incidence that may be expected if a lens receives a given dose in the usual course of therapy. Furthermore, the group of 25 cases in the dosage range from 750 r to 950 r is of sufficient size to make the incidence seem reasonably accurate. Thus, one could expect that if, in the course of therapy, it were calculated that a lens would receive this amount of roentgen or gamma radiation in 3 weeks to 3 months, the patient would have about a 60 per cent chance of developing a cataract. In addition, as is shown in Table III, about half of the cataracts would be progressive with considerable loss of vision. Similar reasoning can be applied to each dosage range with the reservations mentioned above.

3. *Time Cataracts First Observed after Treatment*

The latent period from the time of treatment with roentgen or gamma radiation to

TABLE III

CATARACTS—STATIONARY AND PROGRESSIVE

Treatment Time—3 weeks to 3 months

(Dose in r at lens)

Dose	350 r to 550 r	551 r to 750 r	751 r to 950 r	951 r to 1,150 r	1,151 r and over*
No. of Cases	3	6	15	3	24
Progressive	0	1	6	2	21
Stationary	3	5	7	1	2
Indeterminate	1	0	2	0	1

* Over 1,450 r there were 20 cases, all with progressive cataracts.

the time of the appearance of the lens opacities in humans has been estimated in the literature as from 6 months to 35 years with an approximate average of 2 to 3 years.[2,7,14,23,25] This is a difficult time interval to estimate accurately since most of the cases in the literature and in this present series were not examined routinely. Some of the cataracts reported here were discovered only when the patients complained of impaired vision or during an examination for some other ocular difficulty. Others were discovered in the course of this study during the special follow-up examinations. The only group of patients in this series who had regular examinations were the children with retinoblastomas. The time of onset of cataracts is more accurate for them.

The time at which the cataracts were first observed after the completion of therapy is shown in Table I for each case. The minimum was 4 months and the maximum 28 years, 6 months. This time interval is calculated after the completion of therapy since it is impossible to determine when the injury to the lens was initiated. Because of the lack of regular examinations, the time interval after treatment at which the lens opacities were first noted might be considered as a maximum time of onset.

(A) Effect of Dose for a Given Duration of Treatment on Time of Appearance of Cataract. It has been shown in experimental animals that as the dose increases the time of onset of the cataract decreases, and it seems reasonable to assume that this would hold true for humans.[3,25] An exact correlation is impossible in a clinical study such as this where the follow-up examinations were so irregular. Furthermore, if this time interval is to have real significance, it is necessary to determine the time of onset or appearance of the lens changes for single and multiple treatments and in relation to a given dosage range. The number of cases in each group is somewhat variable, but this is unavoidable. Within the limitations just mentioned, the results seem to show an inverse relationship between dose and the time of appearance of the cataract.

TABLE IV

SINGLE TREATMENTS

RELATIONSHIP OF DOSE TO TIME CATARACTS FIRST SEEN

(Dose in r at lens)

Dosage Range	200 r–650 r	651 r–1,150 r
Average	450 r	800 r
No. of Cases	10	10
Range of Time of Onset	2 yr. 6 mo. to 22 yr. 1 mo.	1 yr. 1 mo. to 8 yr. 7 mo.
Average Time of Onset	8 yr. 7 mo.	4 yr. 4 mo.

The effect of single doses of varying amounts of gamma radiation upon the time of onset of the cataracts is shown in Table IV. The averages for the two dosage ranges show an inverse relationship between dose and the time of appearance of the cataracts in that as the dose increases the latent period decreases. Thus, with an average dose of 450 r at the lens, delivered in a single treatment, the average time of the clinical appearance of the lens changes was 8 years, 7 months. When the single dose was an average of 800 r at the lens, the average time of onset was 4 years, 4 months. In this study there were no persons whose lenses received over 1,150 r in a single treatment.

A comparison of the effect of single and multiple or fractionated treatments and varying durations of treatment on the time of onset of a radiation cataract is of interest. The results are shown in Table V. In this table the cases have been grouped according to five dosage ranges and three durations of treatments. In this way similar cases can be compared. The children under one year of age have been excluded. The reason for this is that their lenses may be more sensitive, as will be discussed below. Also excluded from Table V are the cases of retinoblastoma, since these chil-

TABLE V

RELATIONSHIP OF DOSE AND DURATION OF TREATMENT TO AVERAGE TIME CATARACT FIRST SEEN

(Dose in r at lens)

Dosage Range	200 r–350 r			400 r–1,000 r			1,001 r–2,000 r			2,001 r–4,000 r			over 4,000 r	
Duration of Rx	Av. Dose	No. Cases	Av. Time	Av. Dose	No. Cases	Av. Time	Av. Dose	No. Cases	Av. Time	Av. Dose	No. Cases	Av. Time	No. Cases	Av. Time
Single	250 r	4	11 yr. 8 mo.	650 r	14	5 yr. 3 mo.	1,100 r	2	4 yr. 2 mo.					
3 Weeks to 3 Months				650 r	9	6 yr. 6 mo.	1,600 r	10	5 yr. 2 mo.	3,050 r	9	2 yr. 8 mo.	4	2 yr. 6 mo.
Over 3 Months				700 r	3	10 yr. 8 mo.	1,450 r	7	6 yr. 2 mo.	2,150 r	2	4 yr. 4 mo.	7	3 yr. 6 mo.

dren had regular eye examinations. This fact, irrespective of other factors, makes their time of onset shorter than for the group that did not have periodic ocular examinations.

(a) *Single Treatments.* In the dosage range from 200 r to 350 r (average 250 r) there were 4 cases with an average time of appearance of the lens changes of 11 years, 8 months. In a higher dosage range there were 14 patients whose lenses received from 400 r to 1,000 r (average 650 r) in a single treatment. The average time of onset or clinical appearance of the cataracts was 5 years, 5 months.

(b) *Divided Treatments (3 weeks to 3 months).* The effect of increasing doses of fractionated radiation delivered in 3 weeks to 3 months is also shown in Table v. There were 9 cases in the dosage range from 400 r to 1,000 r at the lens (average dose 650 r) which showed an average time of clinical appearance of the cataracts of 6 years, 6 months after the completion of therapy. In the next higher dose range from 1,001 r to 2,000 r (average 1,600 r), there were 10 cases with an average time of onset of 5 years, 2 months. A group of 9 persons whose lenses received 2,001 r to 4,000 r (average 3,050 r) showed an average time of clinical appearance of the lens opacities of 2 years, 8 months. In the 4 cases where the dose to the lens was over 4,000 r the average time at which the cataracts were first seen was 2 years, 6 months. Thus, there was an inverse relationship between the dose and the time of appearance of the lens changes—the higher the dose the shorter the latent period before the cataracts appeared.

(c) *Divided Treatments (over 3 months).* Table v also shows the effects of increasing doses of divided treatments over a period greater than 3 months on the time of appearance of the lens opacities. In the dosage range from 400 r to 1,000 r (average 700 r), there were 3 cases with an average time of onset of 10 years, 8 months. In the next dosage range—1,001 r to 2,000 r (average 1,450 r), there were 7 cases with an average time of onset of 6 years, 2 months. In the dosage range from 2,001 r to 4,000 r (average 2,150 r), there were 2 cases with an average time of onset of 4 years, 4 months. In a group of 7 patients whose lenses received over 4,000 r, the average time of the appearance of the cataracts was 3 years, 6 months. The fact that the latent period decreases as the dose increases is again apparent.

(B) Effect of Varying Durations of Treatment for a Given Dose on Time of Appearance of Cataract. The effect of increasing protraction of treatment for a given dose on the time of onset or clinical appearance of a radiation cataract is also indicated in Table v. The number of cases in some of the groups is small, but, nevertheless, the general tendency seems to be that for any dosage range with increasing duration of

treatment the time of appearance of the cataracts is delayed. Thus, in the dosage range from 400 r to 1,000 r, the average time of onset for the 14 cases in the single treatment group was 5 years, 3 months. In this same dosage range with a treatment time of 3 weeks to 3 months, the average time of onset was 6 years, 6 months. When the radiation was given over a longer time, the average time of appearance of the lens changes was further delayed. Although the number of cases in each group was small, the figures seem to allow these conclusions to be drawn: (1) the higher the dose, irrespective of duration of treatment, the more rapidly the cataract will develop and (2) within the dosage levels studied the more the radiation is fractionated the longer the latent period for the development of the lens opacity.

4. *Relationship of Dose to Progression of Cataracts*

It is of considerable importance clinically to know whether or not for a given dose a cataract is likely to remain stationary or to progress. In this study progressive signifies those lenses in which the opacity continued to increase so that ultimately the lens became completely opaque with a corresponding decrease in vision. In many instances small early opacities will progress for several months and then become stationary with little effect on vision. These have been classified as stationary.

The indeterminate cases are those which had only one eye examination within such a short time after treatment that the ultimate status of the lens could not be determined or cases in which complicating factors developed after the appearance of the radiation cataract (hemorrhage, surgery, glaucoma or uveitis) which could have been responsible for the progression. In order to evaluate accurately the data, it is necessary to compare lenses that received comparable doses delivered over a similar period.

Because of the lack of regular eye examinations and since some of the cataracts were discovered only because the patients complained of impaired vision, the relative incidence of stationary and progressive opacities may be weighted in favor of the latter. It is possible that there are some stationary, asymptomatic cataracts that have gone undiscovered.

In Table VI are shown the results for the 20 cases which received the total radiation to the lens in a single treatment. In the dosage range from 200 r to 650 r (average 450 r) there are 10 cases. Three of the cataracts progressed, 6 remained stationary and 1 was indeterminate. In the higher dosage range—651 r to 1,150 r (average 800 r), there are also 10 cases of which 7 showed a progressive type of lens opacity, 2 remained stationary and 1 was indeterminate. In this series it would appear that the higher the dose delivered in a single treatment the greater the incidence of a progressive type of cataract.

The effect of dose and duration of treatment on the production of progressive or stationary opacities is shown in Tables III and VII. In Table III the cases are divided into the same dosage intervals as in Figure 9. It is evident that as the dose increases the percentage incidence of progressive opacities increases. Above 1,450 r at the lens all the cataracts were progressive. In Table VII the single doses are divided into dosage ranges different from

TABLE VI

CATARACTS—STATIONARY AND PROGRESSIVE
Effect of Single Treatment
(Dose in r at lens)

Dosage Range	200 r–650 r	651 r–1,150 r
Average Dose	450 r	800 r
Number of Cases	10	10
Progressive	3	7
Stationary	6	2
Indeterminate	1	1

TABLE VII

CATARACTS—STATIONARY OR PROGRESSIVE*
Effect of Varying Doses and Duration of Treatment
(Dose in r at lens)

Dosage Range	200 r–350 r				400 r–1,000 r				1,001 r–2,000 r				2,001 r–4,000 r				over 4,000 r		
Duration of Treatment	Av. Dose	No. of Cases	Progressive	Stationary	Av. Dose	No. of Cases	Progressive	Stationary	Av. Dose	No. of Cases	Progressive	Stationary	Av. Dose	No. of Cases	Progressive	Stationary	No. of Cases	Progressive	Stationary
Single	250 r	3	0	3	650 r	13	8	5	1,100 r	2	2	0							
3 Weeks to 3 Months					750 r	14	2	12	1,600 r	10	7	3	3,050 r	8	8	0	5	5	0
Over 3 Months					750 r	4	2	2	1,450 r	6	2	4	2,400 r	4	4	0	8	8	0

* Indeterminate cases and patients under 1 year of age omitted.

Table VI in order to compare them with the other durations of treatment. The indeterminate cases have been omitted. The retinoblastoma cases over one year of age have been included since the regularity of their eye examinations was not a factor in whether the cataracts remained stationary or progressed.

There were 14 cases, in the dosage range from 400 r to 1,000 r, in which divided treatments were given from 3 weeks to 3 months. Two of the cataracts were progressive and 12 were stationary. For this same duration of treatment, as the dose increased the incidence of progressive opacities increased. Thus, in the dosage range from 1,001 r to 2,000 r, 7 of 10 determinate cases developed progressive cataracts and only 3 remained stationary. In the higher dosage ranges for the same treatment time, none of the cataracts was stationary. In the group with a treatment time greater than 3 months, the number of cases under 2,000 r was smaller. However, in the 12 cases with a dose to the lens of 2,000 r or more, all of the cataracts were progressive.

The effect of protraction of therapy for a given dosage range is also apparent in Table VII. At the dosage level of 400 r to 1,000 r in the single treatment group, 8 of 13 cases developed a progressive type of opacity. When the same dose was delivered in 3 weeks to 3 months, 2 of the 14 cases showed this type of lens change.

At the next higher dosage level, 1,000 r to 2,000 r, there were 2 cases in the single treatment group and both were progressive. There were 10 cases with a treatment time of 3 weeks to 3 months of which 7 developed progressive cataracts. In the group with a treatment time greater than 3 months, there were 6 cases of which 2 had progressive opacities. In the higher dosage ranges, irrespective of the degree of protraction of therapy, all of the cataracts were progressive.

The effect of fractionation and protraction of treatment upon the progression of a cataract is also shown by determining the point at which there is a 100 per cent incidence of progressive changes for each of the three groups shown in Table VII. For the cases with single treatments all of the lenses that received over 700 r developed progressive opacities. There were 6 of these in this group. When the duration of treatment was 3 weeks to 3 months, the 100 per cent incidence was not reached until 1,450 r. In this group there were 20 cases with doses to the lens greater than this. When therapy was protracted over 3

months, this critical level was reached at 2,150 r, and there were 13 cases with doses greater than this.

5. *Relative Sensitivity of Young Lenses*

It has been assumed as the result of experimental work on animals[8] that the lenses of children are more radiosensitive than those of adults. The most recent study of this type was that of Cogan and Donaldson[3] on rabbits.

This question is of obvious importance since radiation is frequently given to or near the eyes of children for various types of benign and malignant lesions. If the young lens has a greater sensitivity to ionizing radiation, it might be expected to manifest this in one or more of the following ways: (1) a cataract should result from a lower dose than for adults or the children should have a higher incidence at a given dose; (2) the lens opacity should appear earlier for a given dose and duration of treatment; and (3) a higher percentage of the cataracts in children should become progressive for the same dose and treatment time.

In a clinical study such as this with a wide diversity of ages, dosage and duration of treatment, it is difficult to interpret the data available. In respect to dosage alone there is evidence to suggest that the very young lenses are more sensitive. In the single treatment group there were no children. In the histogram shown in Figure 9, there are 29 children under 6 years of age and 11 adults in the dosage range of 530 r to 1,050 r. The incidence in the group of 11 children under one year of age is 73 per cent, and for the group of 18 children from 1 to 5 years of age it is 50 per cent. The incidence for the group of 11 adults is 64 per cent.

The 8 children under one year of age with cataracts whose lenses received from 560 r to 900 r (most frequent dose 900 r) in 3 weeks to 3 months had an average time of onset of 2 years, 7 months with a range of 1 year, 7 months to 4 years, 1 month. About two thirds of the cataracts were progressive (Table VIII).

There were 9 children from 1 to 4 years of age with cataracts in the dosage range 650 r to 900 r (most frequent dose 900 r). In this group the average time of onset of the lens opacities was 3 years, 8 months, with a range of 1 year, 8 months to 6 years, 9 months. About one quarter were progressive. Although the two groups were small, it would appear that the lenses of the children under one year of age showed a higher incidence of cataracts which developed more rapidly with a larger percentage of progressive opacities.

All of the children had regular eye examinations so that the time of onset and whether the cataracts were stationary or progressive is reasonably accurate. These should be compared to a group of adults

TABLE VIII

EFFECT OF AGE ON TIME OF ONSET AND INCIDENCE OF PROGRESSIVE OPACITIES
Treatment Time 3 Weeks to 3 Months
(Dose in r at lens)

	Children under 1 Yr.	Children 1–4 Yr.	Adults
Average Age	6 mo.	2 yr. 1 mo.	64 yr.
Dosage Range	560 r–900 r	650 r–900 r	530 r–1,050 r
Average Dose	770 r	850 r	790 r
Number of Cases	8	9	6
Average Time of Onset of Cataract	2 yr. 7 mo.	3 yr. 8 mo.	3 yr. 11 mo.
Progressive	5	2	1
Stationary	3	6	2
Indeterminate	0	1	3

with the same approximate dosage and treatment time. As stated before, the adults did not have regular eye examinations. However, all of the adult cataracts shown in Table VIII were found within 5½ years after therapy except for one stationary case which had the first eye examination 19 years, 4 months after therapy. This case has been omitted because of the long time interval without eye examinations. The dose to the lens was from 530 r to 1,050 r (most frequent dose 800 r). The average time of onset of the cataracts was 3 years, 11 months, with a range of 1 year, 2 months to 5 years, 6 months and one of the determinate cases was progressive. This would tend to suggest that in this series the lenses of the children over one year of age had somewhat the same sensitivity as those of the adults.

SUMMARY

The dose of roentgen and gamma radiation to the lens has been measured for 100 cases with radiation cataracts and 73 cases which received radiation to the lens but did not develop cataracts. The measurements were done on a special phantom which has been described. The cases have been divided into three groups—single treatment, divided treatment 3 weeks to 3 months, and divided treatment over 3 months. The minimum cataractogenic dose for each group was 200 r, 400 r, and 550 r, respectively.

The incidence of cataracts for the group with the treatment time of 3 weeks to 3 months has been shown and its significance discussed. Thus, if a dose of 750 r to 950 r were delivered to a lens in 3 weeks to 3 months, there would be approximately a 60 per cent probability that a cataract would develop and about a 50 per cent chance that it would be progressive with a corresponding loss of vision. All cases which received over 1,150 r to the lens, irrespective of the duration of treatment, developed cataracts. The 100 per cent incidence level occurred at the lowest dose for the single treatment group. In the cases with multiple treatments, the longer the duration of treatment the lower the incidence at a given dosage range below 1,150 r.

The effect of dose and varying treatment times on the time of onset and progression of cataracts has been considered. The higher the dose for a given duration of treatment, the shorter the time of appearance of the lens changes and the higher the incidence of progressive opacities. In general, fractionation delays the time of onset of cataracts and results in fewer severe opacities. The lenses of children under one year of age appear to be more sensitive to radiation than those of older children and adults.

It should be emphasized that the usual shielding methods are ample protection for the lens from roentgen rays of 100–140 kv. (half-value layer 1–5 mm. Al). When higher voltages are employed (200–250 kv. —half-value layer 1–2 mm. Cu), 2 mm. of lead will usually suffice for the tumor doses currently employed. In the retinoblastoma cases with the lower doses being used at present and with care in positioning the ports, radiation cataracts will be seen less frequently. Furthermore, in these cases it is of necessity a calculated risk.

In the single treatment group all of the cases were basal or squamous cell carcinomas treated with radium plaques. This method of therapy, in which adequate protection cannot be provided, is seldom used at present. Gold seeds for the treatment of these lesions or hemangiomas of the lids and face have largely been replaced by low voltage radiation where better protection can be provided. Furthermore, the low doses necessary for the treatment of hemangiomas make this complication less likely.

In the entire group of 100 radiation cataracts, it is estimated that by the use of current treatment techniques the lens opacities could have been avoided in at least 80 cases.

George R. Merriam, Jr., M.D.
635 West 165th Street
New York 32, New York

Elizabeth F. Focht, B.A.
444 East 68th Street
New York 21, New York

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RADIATION THERAPY IN THE TREATMENT OF RETINOBLASTOMA*

By IVOR G. WILLIAMS, M.B., F.R.C.S., F.F.R., D.M.R.E.
St. Bartholomew's Hospital
LONDON, ENGLAND

THE problems posed by retinoblastoma are at the same time perplexing, fascinating and tragic. It is a rare tumor with an incidence of 1 in 34,000 live births and some 3 in 10,000 first consultations in ophthalmic centers. Few people have experience of considerable numbers of cases, and the statistical analysis of results of treatment is even less easy than in commoner conditions. It is a congenital tumor and 60 per cent become manifest during the first three years of life, while only about 5 per cent occur after the age of six years. Children cannot complain of symptoms, so that by the time the gray-white fundus reflex is seen, the growth is large enough to be diagnosed by ordinary methods of examination, appearing on the retina as a flocculent white tumor with a granular surface which is crossed by thin looped blood vessels. Although sporadic cases are most common, familial and hereditary cases occur. In the St. Bartholomew's Hospital series there are records of one family where all the children were affected, and in other groups it affected three generations. The mode of transmission is irregular. The risk to the children of an affected parent is very high; the risk to a second child of normal parents is said to be about 1 per cent. Spontaneous regression can occur and Stallard records such a case where retrogression occurred after an attack of scarlet fever. The patient subsequently had 2 children, both of whom had bilateral tumors, one of whom is recorded in this series treated by radon seeds. In about 20 per cent the disease is bilateral, most often in hereditary and familial cases. The disease in the second eye is a true new formation, and although they may coincide, one tumor is much more advanced than the other. The maximum period recorded for the interval between the appearance of first and second tumors is eleven years (Maghy, 1919).

PATHOLOGY

The growth arises probably from cell rests of the primitive neuro-ectoderm which forms the optic vesicle, and originates in either the inner or outer nuclear layer of the retina, appearing as a single or multiple nodules. It can protrude forward into the vitreous as a flocculent friable mass which Stallard compares to cream cheese, or it can insinuate itself between the two layers of the retina (the rodcones and the pigment layers) or in both directions. Cells washed off the surface can travel in the intra-ocular fluids and graft in the ciliary body, the iris or the filtration angle. From here fungation occurs through the corneoscleral junction producing a huge fungating vascular necrotic tumor on the face of the child—the fungus hematodes of earlier writers.

The most important extension, however, is backwards towards the brain via the optic nerve. The nerve may be directly infiltrated, thus destroying it, or extension occurs along the sheath so that ultimately the cerebral subarachnoid space is reached. In either case it will then spread rapidly, seeding itself throughout the central nervous system or forming a sheet of growth over the surface of the brain and cord. Metastasis by the lymphatic channels only occurs when the orbit is involved, while blood stream metastases, most often to bone, are very uncommon. Death of the patient most commonly occurs due to its intracranial extensions.

The tumor consists of small, round cells,

* Presented at the Thirty-eighth Annual Meeting of the American Radium Society, Houston, Texas, April 9–11, 1956.

many undergoing mitosis. Areas of necrosis are common, and frequently calcification may be seen in the degenerate areas. Parts of the tumor may show differentiation in the form of rosettes or fibrillated areas or both, simulating the rod and cone layer of the normal retina. Reese considers rosettes to be an indication of a slower rate of growth and a somewhat less malignant type. It is interesting to compare these features, *i.e.*, calcification and rosettes, with two other tumors in children both of nervous system origin—neuroblastoma and medulloblastoma. Spontaneous retrogression also occurs in neuroblastoma.

PROGNOSIS

Retinoblastoma is a rapidly growing, highly malignant tumor. The classic treatment of unilateral disease is enucleation of the eye, the result here depending entirely upon the condition of the optic nerve of the excised eye. A long part of the optic nerve must be obtained in order to place the section behind any nerve invasion. In a series of 116 eyes, Reese (1951) found such extension in 27 per cent, and in 8.5 per cent it was beyond the line of excision. A most important point is that extension towards the brain may not be in continuity, but islands of growth may be separated by apparently unaffected parts of optic nerve. In 95 per cent of patients with unsuccessful enucleation, orbital recurrences will develop within eighteen months. The outlook in these cases is very grave, although a few long survivals have been recorded. If the nerve is not invaded prognosis will then depend upon whether or not a tumor develops in the other eye. While there may be agreement as to the indications for enucleation in unilateral disease, when it is bilateral considerations become more difficult. In these cases the disease is usually more advanced in one eye than the other, and it is, therefore, justifiable to attempt to conserve vision in the less affected eye, if this can be done without jeopardizing the life of the patient. It follows also, as a corollary, that there is no object in keeping an eye which is blind or where the results of treatment result in blindness. It is for these reasons and as a result of this experience that Stallard advises excision if one third or more of the retina is involved in growth, and the other eye is normal or less extensively involved than its fellow. He refers his surgically treated patients for postoperative roentgen therapy to the orbit of the affected side despite the risk of inducing a contracted socket following such therapy.

RADIATION THERAPY

From our knowledge of the natural history of the disease it is evident that treatment by irradiation may be called for under a variety of circumstances: (1) unilateral disease; (2) bilateral disease; (3) postoperative, when the pathologist reports involvement of the optic nerve; and (4) definite orbital recurrences, not yet extending to the brain.

In this paper we are only concerned with the primary tumor in the eye.

As in all other neoplastic processes, the aim of radiation therapy is the homogeneous irradiation of the tumor-bearing volume to adequate dosage with sparing of the normal tissues. Retinoblastoma presents many problems from the point of view of technique because of its site of origin and the natural history of the disease. Retinal tissue has long been used by radiobiologists for investigation of radiation effects both *in vivo* and *in vitro*. The nervous tissues from which it arises and the sclera on which it rests are highly radioresistant. But the problem is complicated since the tumor is situated in the posterior part of the eye, and the normal tissues anterior to it, the lens, the uveal tract and the cornea, have relatively low thresholds for radiation damage. It is, therefore, desirable to strike the neoplasm with a dose which will destroy it without producing irremediable damage to the eye. In an attempt to bring a small radioactive source

as near as possible to the tumor, Foster Moore, in 1929 at St. Bartholomew's Hospital, inserted a small radon seed directly into the tumor through a stab incision of the sclera. He used a special angular double-edged knife, the width being equal to the diameter of the radon seed, which was introduced into the incision at the base of the neoplasm. He abandoned this technique when he found that the growth might be pushed forward by the seed, and he then tried suturing the seed on to the sclera. This had the disadvantage that the radon containers ride at a tangent to the sclera, giving an uneven radiation, intense at the site of fixation and falling off rapidly where the straight seed was not in contact with the sclera. In 1934, Stallard, at St. Bartholomew's Hospital, introduced a technique in which he sutured to the sclera a stent strip with one, two, or three radon seeds embedded in it. This had the advantage that the radon could be brought close to the optic nerve sheath, a point where technically it was most difficult to suture a seed. Between 1934 and 1948, Stallard treated 15 patients and during this time carried out a thorough clinical and pathologic study of the effects of radiation on retinoblastoma.

CLINICAL RESULTS OF RADON TREATED CASES

Foster Moore's Series. Five patients were treated from 1929–1934. One died postoperatively from gastroenteritis. Four are alive and well to date, that is, 22 to 27 years later. Two are blind, 1 from endophthalmitis and 1 from intra-ocular hemorrhage, iridocyclitis and glaucoma which occurred eleven months after successful irradiation. Two have sufficient vision despite cataract to enable them to earn a living.

Stallard's First Series. Fifteen cases were treated (up to 1948). All were under three years of age; 14 had bilateral tumors. The size of the growth was over half the interior of the globe in 1 case, nearly half in 1, one quarter in 2. There were four islands of growth in 2 cases, three in 3 cases and two islands in 1. The macula was involved in 4 cases. Radon dosage was planned according to the size of the neoplasm, 2 cases had one 2 mc seed, 4 had 3 seeds and one had 4 seeds. Two applications were necessary in 6 cases and three in 3 cases, and three of these were for a new island of glioma, arising later and away from the site of the original growth. Stallard also re-treated the original site in 4 instances because he was not satisfied that the original treatment had destroyed the growth. Although the majority disappeared in one to two months, he found in others that it was necessary to wait five or six months to be sure that the effect was complete.

Out of the 15 cases, 1 died from an unknown cause one year after irradiation. There was no trace of the growth to be found on pathologic examination of the eye after death. It was suggested that this patient died from the cerebral effects of irradiation given to the other orbit after excision of the other eye. Fourteen are alive today. One had the eye excised in Manchester for a suspected recurrence. One with unilateral disease lost her sight in this eye from a retinal detachment and hemorrhage. Three others are blind from similar causes. Nine patients (or 60 per cent) had sufficient sight for educational purposes. They could attend school, pass examinations and play games.

THE REACTION OF RETINOBLASTOMA TO IRRADIATION

Macroscopically the effects of radiation become evident about the third day of treatment. The growth becomes more densely white, especially around its edges, looking rather like curdled milk. In the second and third weeks shrinkage is obvious and this continues up to the tenth week. Some of the growth may separate during this time and gravitate away from the main mass ultimately becoming absorbed. A characteristic scar is left at the site of the neoplasm; it is flat and white

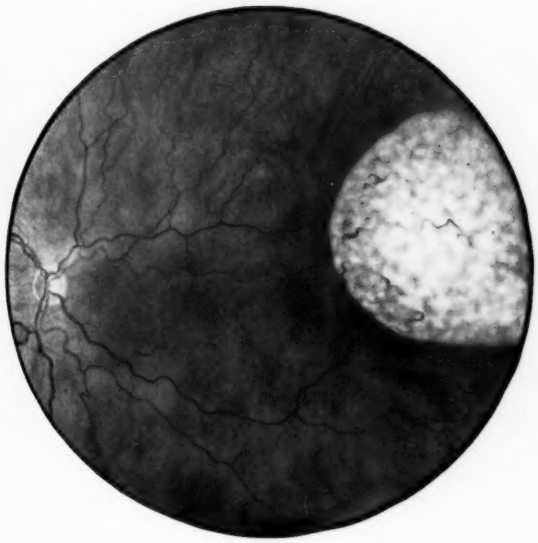

Fig. 1. Glioma of the retina before treatment.

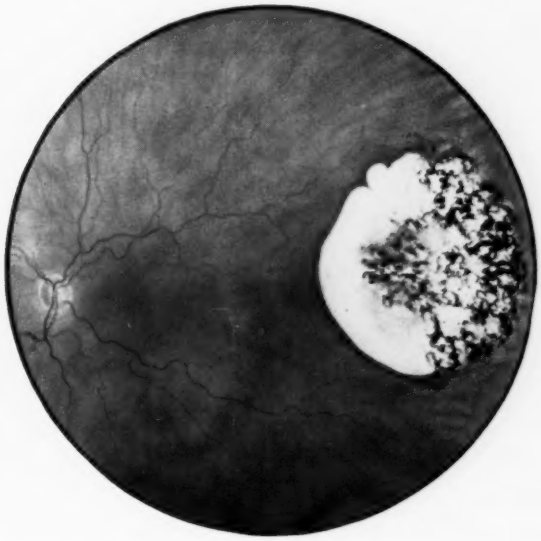

Fig. 2. Glioma of the retina after treatment.

and has a serrated edge fringed with pigment. The nearby retinal vessels are occluded, and the surrounding fundus becomes stippled with pigment (Fig. 1 and 2). If the growth does not entirely disappear within three months after the treatment, a second application may be necessary.

Histologically, characteristic radiation changes are seen in the retinoblastoma cells including pyknosis, lobulation karyorrhexis, with finally destruction of the cell. A striking feature is the vascular changes. There is a reduction in the general vascularity of the choroid and retina. Some vessels are collapsed, others varicose and full of blood. The area of retina exposed to radiation becomes atrophic and disorganized, and in a few cases one can see irregular clumps of disorganized retinoblastoma cells compressed by fibrous tissue. Other changes include edema, fibrosis, deposits of exudate and pigment, calcification and retinal hemorrhages.

COMPLICATIONS

From the foregoing description of the changes induced by irradiation the main complications which occurred can be readily appreciated in the series of 15 cases treated up to 1948. These were as follows:

1. *Retinal Changes:* (a) *Exudates.* In those where heavy doses had been given, in 5 cases grayish irregular shaped exudates could be seen in and around the macula. The onset of these varied from seven months to eleven years and persisted for many years. Other complications set in in these particular patients but the exudates contribute to a diminution of vision. (b) *Hemorrhage.* This was a late complication of 6 cases. The majority occurred between six and twelve months after treatment and seemed to be associated with the proximity of the radon seeds to the main branches of the central retinal vessels. It varied from a small leak, diffuse choroidal and subretinal hemorrhages to severe bleeding into the vitreous body. (c) *Detachment.* This occurred in 4 cases. They were treated in 1936–1937, and had one half or more of the retina involved. None of these have any evidence of recurrence to date and the appearance of the detachment suggested that a mass of debris had collected between the retina and the choroid.

2. *Lens: Cataract.* In 5 patients irradiation cataract occurred in the lens, in

4 it lay in the central part of the posterior cortex. Here again this complication occurred in those given high dosage, in 4 the treatment having been repeated. The onset appeared between two and eleven years after treatment and it was slowly progressive.

The serious complications of total retinal detachment, severe intra-ocular hemorrhage and complicated glaucoma occurred in eyes where the growth occupied more than half the retina. Stallard suggests that the eye cannot withstand the breakdown of so much growth in a confined space and the toxins produce endophthalmitis.

In 1948 Stallard, from his experience of the previous twelve years, was thus in a position to assess the value of this method of treatment. His conclusions were as follows:

1. The growth is radiosensitive, its parent tissue radioresistant.
2. In the successful case both sight and life could be saved.
3. Complications occurred due to three factors: (a) the breakdown of the tumor; (b) the vascular changes; and (c) irradiation of the normal tissues in front (the lens).
4. The success of radiation therapy by this method depended almost entirely upon the size of the neoplasm at the time of treatment, and the method is unsuitable if one half or more of the interior of the eye is occupied by tumor, or the radium has to be placed over the large branches of the central retinal vessels as these curve near the optical disk.

TABLE I

RADON TREATMENT OF GLIOMA RETINAE

Size of Growth		No. and Strength of Radon Seeds (applied 168 hours)	No. of Cases Treated	Dose at Apex of Growth	Minimum Dose in Region of Tumor at a Level 1 mm. inside Surface of Sclera
Dia. mm.	Height (Estimated) mm.				
3	2.5	1×2 mc	4	8,800 r	23,400 r
		2×1.1 mc	2	9,050 r	22,600 r
4.5	3	1×2 mc	1	7,050 r	15,700 r
		3×1.1 mc	1	10,900 r	30,200 r
5	3.5	1×2 mc	5	5,800 r	13,900 r
7	5	1×2 mc	4	3,500 r	9,500 r
		2×2 mc	1	6,300 r	12,900 r
8	5.5	1×2 mc	1	3,350 r	7,600 r
10	7	2×2 mc	2	4,350 r	8,500 r
21	13	4×2 mc	1	2,900 r	12,300 r

In all cases treated with 2 mc seeds:

	Where 1 seed used	Where more than 1 seed used
Maximum dose at a level 1 mm. inside surface of sclera.	38,500 r	50,000 r
Maximum dose where seeds touch sclera.	125,000 r	150,000 r

DOSAGE

Further progress depended upon an accurate assessment of the physical conditions under which these patients had been treated. With the help of Mr. G. S. Innes and Mr. F. S. Stewart, physicists to the Radiotherapy Department, these cases were reviewed in order to form an estimation of the radiation dose received at various points. The eyes were arranged according to the size of the glioma; the diameter is the dimension measured along the spherical surface of the retina and the height is the distance to the apex of the tumor from the retinal level. This measurement cannot be absolutely accurate and must of necessity be an estimated height.

The calculations in Table 1 showed that where the radon seed lay in contact with the outer surface of the sclera the dose varied between 125,000 r and 150,000 r, depending on the number of seeds. At the base of the glioma on the retina, the dose was very uneven, depending on the combined thickness of sclera, choroid and retina; but on a spherical surface 1 mm. thick it varied between 38,500 r and 50,000 r. The lowest dose will be at the apex, and this dose is governed by the estimated height. Here it varied between 3,000 r at 13 mm. (4×2 mc seeds) to 10,000 r at 3 mm. (3×1.1 mc seeds). It may well have been that the smaller growths received more than the estimated dose as the assessment of height cannot be accurate. The problem was thus posed for the construction of an applicator where the following requirements had to be fulfilled: (1) the minimum dose to the tumor shall be 4,000 r in seven days; and (2) the dose to the sclera must be as low and as uniform as possible (Fig. 3).

This implied the use of more distributed sources of radiation rather than discrete sources such as radon seeds.

Two other essentials were that the applicator must be thin, smooth and non-irritating, while lastly the dose to the surgeon's hands should be kept as low as possible, and quickness of application with the radioactive source was imperative.

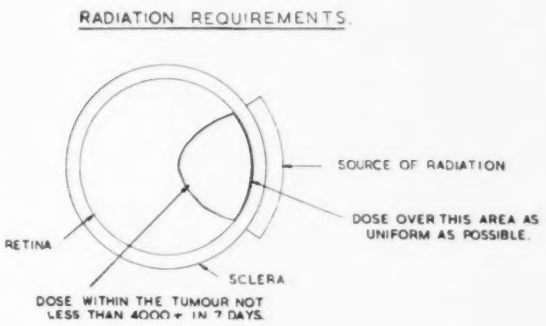
RADIATION REQUIREMENTS.
SOURCE OF RADIATION
DOSE OVER THIS AREA AS UNIFORM AS POSSIBLE.
RETINA
SCLERA
DOSE WITHIN THE TUMOUR NOT LESS THAN 4000 r IN 7 DAYS.

FIG. 3

CONSTRUCTION OF APPLICATORS

Based on measurements taken from eyes removed at operation the following average measurements were accepted: (1) the diameter of the average eye is 22 mm.; (2) the sclera and choroid are 1.5 mm. thick; (3) the height of the glioma in these cases under consideration averaged two-thirds of its maximum base diameter. Hence, from the applicator surface the maximal lesion height is (1.5+2/3 diameter) mm.; and (4) the average inner radius of curvature of an infant's eye is 11 mm. (Fig. 4).

Radium applicators, called disks, were thus constructed. The disks have a platinum casing in the form of a segment of a spherical shell 1.3 mm. thick, the inner radius of curvature being 11 mm. The wall thickness is 0.5 mm. of platinum, thus leaving a well 0.3 mm. thick in the center. A range of applicators suitable for irradiating areas from 5 to 15 mm. in di-

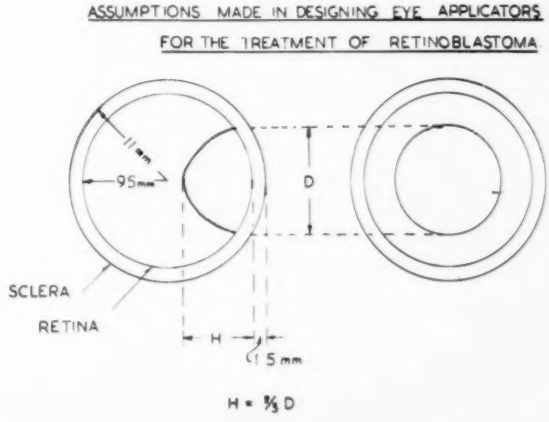

FIG. 4

ameter was constructed, the radium loading varying from 0.5 to 5 mg.

The edge of the disk is grooved along its entire circumference, and it fits closely into the groove of a similarly curved semicircular clip, where it is retained by a silk suture which passes through holes at the ends of a lug on the clip and is then drawn taut in the exposed groove around that part of the disk which is not in contact with the semicircular clip. Two other lugs, also curved like the disk, project one from each end of the clip; these are drilled for the retention of scleral sutures which secure the clip, and thus the disk, to the eye. The lugs may be of various lengths in order to facilitate attachment to the sclera.

The active source contained in the well of the disk was in the form of asbestos impregnated with radium salt. The smaller ones have a flat circle of the source, the larger ones having an annulus as well as a central source in order to achieve homogeneous irradiation. The radium loading of the various sizes was calculated to give 3,500 r in one week at the apex of the glioma. Considerable difficulty was encountered in making these radium applicators owing to gassing of the asbestos during the soldering processes. This led to small blow holes in the solder and radon leakage. Two, however, the 5 mm. 1 mg. and the 10 mm. 2.7 mg. disks, were used clinically but have now been abandoned.

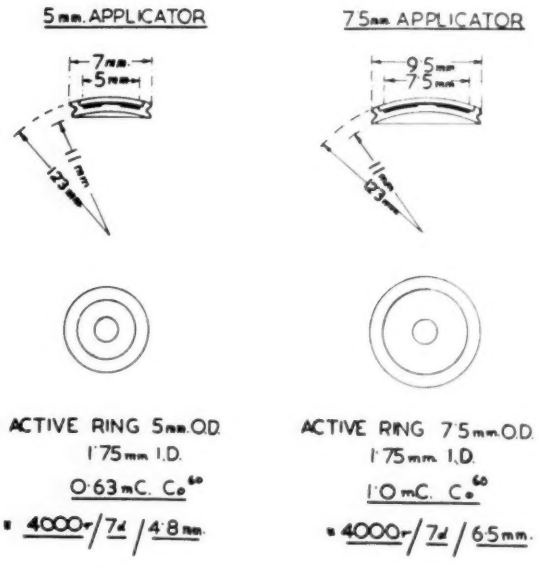

Fig. 5. Construction of applicators.

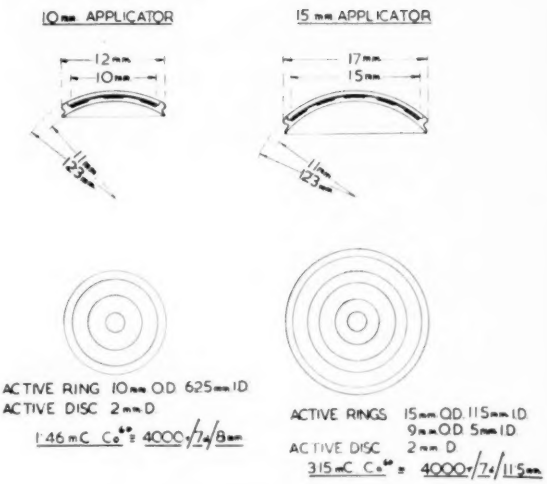

Fig. 6. Construction of applicators.

The present disks are made in two parts of stainless steel which are silver-soldered together when the activated cobalt sources are fitted into the well provided in one of these parts (Fig. 5 and 6). Table II gives the characteristics of these applicators. Corrections will have to be made for the decay of cobalt[60].

Technique of Application

The technique of application is as follows (Fig. 7, 8 and 9): The site of the tumor is exposed through a suitable approach. The media of the eye being transparent, the limits of the growth can be marked out exactly by coagulating a spot in the choroid and retina with a diathermy terminal 2.5 mm. in diameter, using 80 ma. current for 5 seconds. The result is checked through the opthalmoscope, four such marks are made and then measured with calipers bearing a millimeter scale. The appropriate cobalt disk is then chosen and placed over the marked area. The site of the groove on the lugs to fix the clip on the eye is then marked on the sclera with a dot of Bonney's blue. Silk sutures are then inserted through the

TABLE II

TECHNICAL DATA REGARDING Co^{60} EYE APPLICATORS

Active Diameter	Outside Diameter	Max. Lesion Depth	mc Co^{60} Required	r at 2 mm. from Applicator Surface
5 mm.	7 mm.	4 mm.	0.63 mc	19,000
7.5 mm.	9.5 mm.	6.5 mm.	1.0 mc	19,000
10 mm.	12 mm.	8.0 mm.	1.46 mc	19,000
15 mm.	17 mm.	11.5 mm.	3.15 mc	19,000
Construction				
5 mm. Diameter Active Applicator			Co^{60} ring	5.0 mm. outer diameter 1.75 mm. inner diameter 0.2 mm. thickness
7.5 mm. Diameter Active Applicator			Co^{60} ring	7.5 mm. outer diameter 1.75 mm. inner diameter 0.2 mm. thickness
10 mm. Diameter Active Applicator			Co^{60} ring	9.75 mm. outer diameter 6.25 mm. inner diameter 0.2 mm. thickness
			Co^{60} disk	2.0 mm. outer diameter 0.2 mm. thickness
15 mm. Diameter Active Applicator			Co^{60} ring	15 mm. outer diameter 11.5 mm. inner diameter 0.2 mm. thickness 9 mm. outer diameter 5 mm. inner diameter 0.2 mm. thickness
1 mc Co^{60} = 1.43 mg. Radium			Co^{60} disk	2.0 mm. outer diameter 0.2 mm. thickness

The stainless steel is made in two parts, which are silver-soldered together when the activated disks are fitted into the recesses provided in one of the parts. This table gives the characteristics of the applicators.

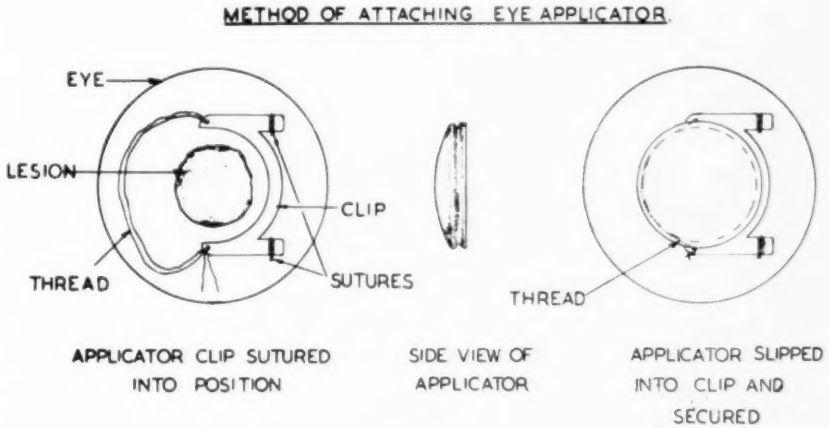

FIG. 7

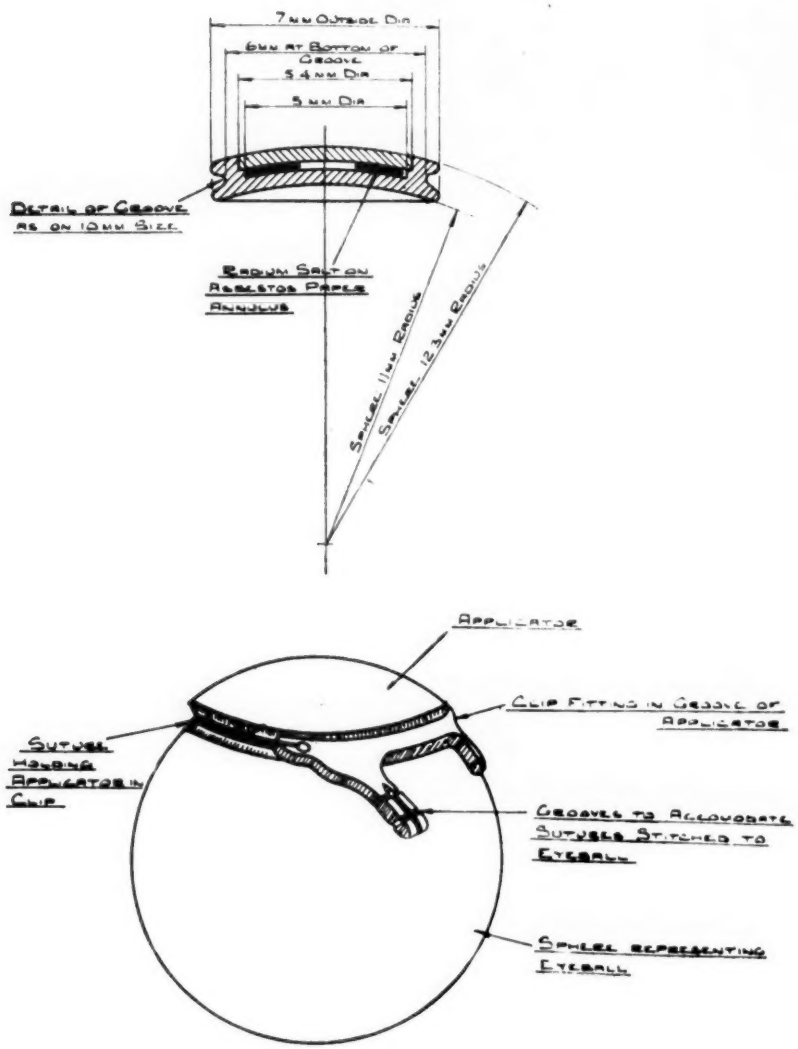
7 MM OUTSIDE DIA.
6 MM AT BOTTOM OF GROOVE
5.4 MM DIA
5 MM DIA
DETAIL OF GROOVE AS ON 10 MM SIZE
RADIUM SALT ON RADIATOR PAPER ANNULUS
SPHERE 11 MM RADIUS
SPHERE 12.3 MM RADIUS
APPLICATOR
CLIP FITTING IN GROOVE OF APPLICATOR
SUTURES HOLDING APPLICATOR IN CLIP
GROOVES TO ACCOMODATE SUTURES STITCHED TO EYEBALL
SPHERE REPRESENTING EYEBALL

FIG. 8. Schematic drawing of fixation of applicator to an eye.

outer half of the sclera at these points, drawn taut, thus securing the clip to the eye. The applicator is then inserted into the arms of the clip and secured in position by looping thread around its groove and tying. These procedures ensure that the lesion is in the center of the field, that the field is the correct size and that the surgeon's hands have minimal exposure to radiation.

RESULTS OF STALLARD'S SECOND SERIES

Mr. Stallard has kindly allowed me to present his latest figures of the results which he has prepared for me in 36 cases treated from 1948 to December 31, 1955 by radioactive cobalt disk therapy.

These cases are subdivided into two groups. 1. Twenty-eight patients (29 eyes, 1 patient having bilateral retinoblastoma) in whom $\frac{1}{3}$ or less of the retina was involved in the neoplasm were treated by radioactive cobalt disks alone. Apparently cured to date are 27 (28 eyes). Of these 20 have vision 6/6–6/18. In 3 the vision is unknown; 5 have the macula destroyed by growth. Six (7 eyes) have survived for five years or longer. Of these 6, 3 children have 6/7 vision; 1 child has 6/9 vision; 1 child

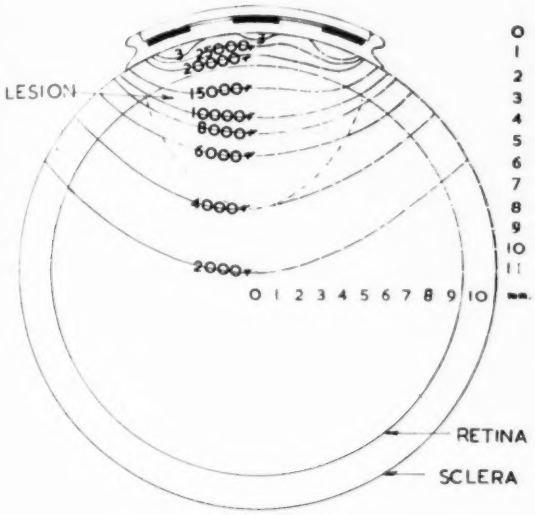

FIG. 9

has 6/18 vision; 1, a Spanish child with both eyes irradiated, has not been assessed yet; 1 became blind, the eye was excised and found to contain no histologic evidence of active growth. This eye had contained 2 large islands adjacent to the optic disk and 3 small islands. Sixteen months after irradiation retinal detachment, glaucoma and endophthalmos occurred.

(In the 1948–1950 patients, 3 children were successfully treated with radioactive disks and had good vision. These have not been included in the successes. They all died from a recurrence from the other orbit for which the eye had been excised in another hospital. One died three months, another 1 year and the third 2 years after successful irradiation of the other eye.)

2. Eight patients have been treated by deep roentgen rays 2,500 r and then by radioactive cobalt disks to the residue of the neoplasm. In all these cases more than half the retina was involved in the neoplasm and so the prognosis was almost hopeless: 1 has some vision; 3 are blind, 2 from total retinal detachment and the other from a vitreous hemorrhage; and 4 have had the blind irradiated eye excised.

SUMMARY

The pathology, prognosis and various aspects of the radiation therapy of retinoblastoma are described.

Clinical results are given for two radon treated series and a Co^{60} disk treated series. The advantage of the latter method is demonstrated.

Radiotherapy Department
St. Bartholomew's Hospital
London, E.C. 1, England

I wish to gratefully acknowledge the permission granted so readily by Mr. H. B. Stallard and the Editor of the *British Journal of Ophthalmology*, to reproduce and incorporate figures and tables from the articles published by him in the Journal. I would also like to thank Mr. Stallard and Mr. George Innes for all their freely given assistance in the preparation of this paper.

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THE ANATOMY OF THE FEMALE PELVIS IN RELATION TO CANCER OF THE CERVIX*

By GRAY H. TWOMBLY, M.D.
NEW YORK, NEW YORK

THE revival of radical surgery as an accepted treatment of cancer of the cervix, which has occurred in the last fifteen years, has focused the attention of gynecologic surgeons sharply on the anatomic details of the structures on the sides and floor of the female pelvis. Simple total hysterectomy requires very little knowledge of the blood or nerve supply of the pelvic organs, since, if one stays close to the cervix, only the uterine artery and veins will be cut, and these can be clamped and tied with little difficulty. The course and position of the ureter is, similarly, of little importance when the dissection is carried downward to the vaginal vault, well medial to this structure. On the other hand, when one begins to dissect out the entire course of the ureter from the pelvic brim to the bladder, to remove all the pelvic lymph nodes on the lateral wall of the pelvis, and expose the hypogastric arteries and veins at their origins, it is imperative that one know exactly the anatomy of the structures involved or suffer the consequences of ureteral injury or unexpected hemorrhage, often of considerable magnitude, difficult to control.

In the course of a fairly extensive experience with radical hysterectomy, we encountered occasionally unexpected metastatic disease in the pelvic lymph nodes. When these seemed easily removable, we did so, but often this was impractical or it was doubted that such removal was complete. One needed then to think about possible subsequent roentgen therapy and this led to frequent marking of the involved sites with silver clips, such as are commonly used by neurosurgeons. When such patients were to be studied by roentgenograms, it was natural to mark the position and length of the cervical canal also. This we did by inserting into it a rubber tandem, such as is used by the Manchester school of radium therapy, the center of which was filled with a suitable length of lead wire. The flanged end of the rubber tandem insured the placing of the lower end of the lead wire exactly at the external os. This technique is mentioned in some detail because such an applicator will stay in the cervical canal without packing and no matter what the patient's position. The applicator can have no possible effect on the position of the uterus.

Position of the Cervix in Relation to External Landmarks. What then were the obvious findings of these studies? First, that the cervix almost always lies above the level of the symphysis pubis; second, that in the lateral position the uterine canal is seen to be at right angles to the vagina, and third, that the regional lymph nodes draining the cervix are much higher than they are usually conceived to be by the roentgen therapist.

We have been impressed from time to time by patients, treated by otherwise competent men, in whom the external treatment portals have been placed too low. Frequently one sees tanning or telangiectasia which involves the groins. The external treatment portals should begin at the top of the symphysis pubis or even above the pubic hair-line. While it is necessary to carry the treatment portals below the symphysis if one is to treat the vagina, it has seemed to us that extension of cervical cancer downward along the vaginal wall is usually superficial in the vaginal mucosa and is better treated with radium in the vagina rather than by external roentgen therapy.

* From the Department of Obstetrics and Gynecology, New York University-Bellevue Medical Center, New York, New York. Presented at the Thirty-eighth Annual Meeting of the American Radium Society, Houston, Texas, April 9–11, 1956.

Corscaden and Butz[2] have emphasized for some time the angle which exists between the uterine canal and the vaginal axis and, in fact, have constructed an applicator which will insert radium into the lateral fornices in proper relationship to the cervix. In the literature, however, this fact is hardly mentioned and one would almost gain the impression that the problem of radium therapy is a two dimensional rather than a very complicated three dimensional one. Particularly is this evident in the use of the conventional colpostat in which the spring joining the two corks is of necessity held by the walls of the vagina in such a position that the most intense rays coming from the corks must be directed backward toward the posterior cul-de-sac and rectal wall. We have endeavored to correct the faulty application of radium inherent in most methods by the construction of an acrylic mold of the distended vagina.[6] In this mold, the radium sources can be placed in the most advantageous positions after adequate roentgenographic study to locate rectum, bladder, uterine canal, and tumor. Holes are drilled in the acrylic in any desired position. Multiple applications can be made with confident assurance that the relative positions of the radium sources will not change. So far, we have been very well satisfied with the results and possibilities for exact treatment with this method.

Position of Pelvic Lymph Nodes in Relation to External Landmarks. The surgeon who does radical pelvic surgery is abashed when he finds metastatic lymph nodes above the bifurcation of the common iliac arteries or around the bifurcation of the aorta. These he doubts he can remove without spilling cancer cells or forcing them further along the lymphatics. He feels that very possibly there are cervical cancers which are radiosensitive enough to respond to the doses which can be given safely with external roentgen therapy. Otherwise, why should we use this form of treatment at all, since the local disease can be handled by radium or surgery. The increased cure rates reported by those who supplement their radium with external therapy confirm him in this opinion. But what does he find? His radiotherapeutic colleague is aiming his portals little higher than the surgeon carries his dissection.

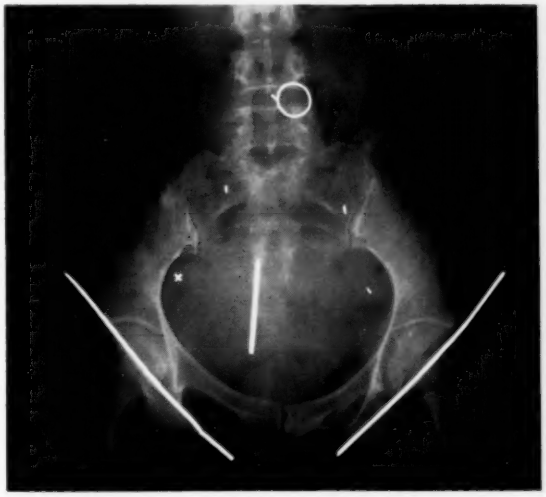

Fig. 1. Location of various structures in the pelvis. The diagonal lead wires lie in the groins over Poupart's ligaments. The vertical wire is in the uterine canal, its lower end exactly at the external os. The circle surrounds the umbilicus. The silver clip to the right of it lies just below the bifurcation of the aorta. The single clips over each sacroiliac joint are in the bifurcations of the common iliac arteries. The clips on the patient's right, in the shape of a cross, lie in the center of the obturator fossa at the location of the "obturator lymph nodes."

We have examined over 50 aortograms taken for one reason or another, most of them on the Urological Service at the Presbyterian Hospital in New York, by Drs. Cahill and Maluf. These films show roughly a third of the patients have the bifurcation of the aorta at the middle of the fourth lumbar vertebra, a third at the top and a third at the bottom with a few scattered cases at the levels of the bottom of the third lumbar or the top of the fifth lumbar vertebra. If one remembers that the fourth lumbar vertebra in a thin woman lies approximately beneath the umbilicus and well above the crests of the ilia, one will begin to extend the treatment fields higher than they are usually given, if the common iliac

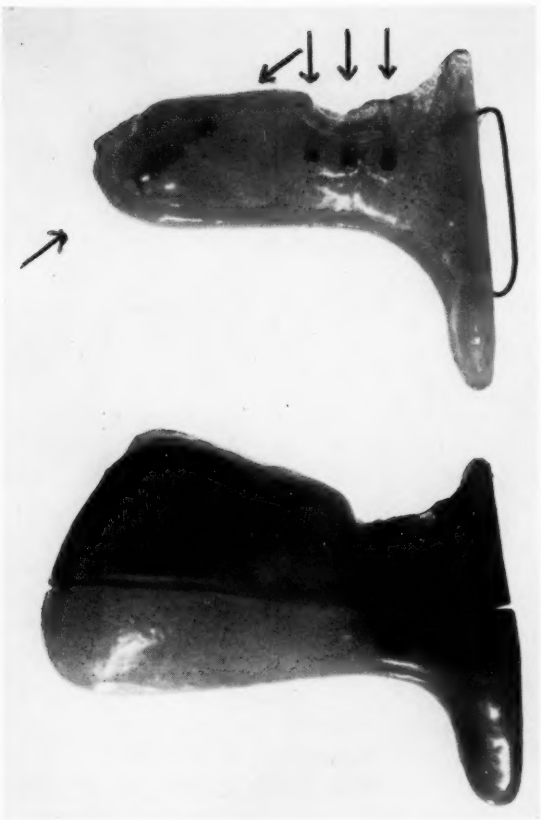

Fig. 2. Two acrylic vaginal molds used in treating cancer of the cervix. Both are made of translucent plastic. The diagonal arrows point to a radium tube buried in the mold in what will be the right vault of the vagina when the mold is inserted. The straight arrows point to three radium tubes arranged to treat a large paraurethral metastasis. The lower mold was made for a patient whose vagina was so big and so bottle-shaped that it was necessary to cut the mold in two pieces and insert it piece by piece.

and paraaortic nodes are suspected of harboring metastatic cancer.

Pelvic Lymph Nodes As Seen at the Time of Radical Surgery. Until we began to employ radical surgery for cancer of the cervix, we were profoundly ignorant of the lymph drainage from this organ. By sectioning lymph nodes removed during radical surgery, we have been made aware of the most common sites of metastasis. The primary lymph drainage seems to be most often to a large lymph node or a series of lymph nodes which lie beneath the external iliac vessels medial to or surrounding asymmetrically the obturator nerve. When the involved lymph node has been located fairly far forward along the course of the nerve, we have spoken of it as an "obturator" lymph node and this is the most common site for metastatic disease. When the lymph node has been up next to the hypogastric vessels or between the external iliac artery and the hypogastric artery, we have designated this as a "hypogastric" lymph node. The next most common site of primary metasases is to the lymph nodes irregularly surrounding the external iliac vessels, particularly the artery. Just to the side of the sacral promontory, one finds the sympathetic chain and ganglia. Along

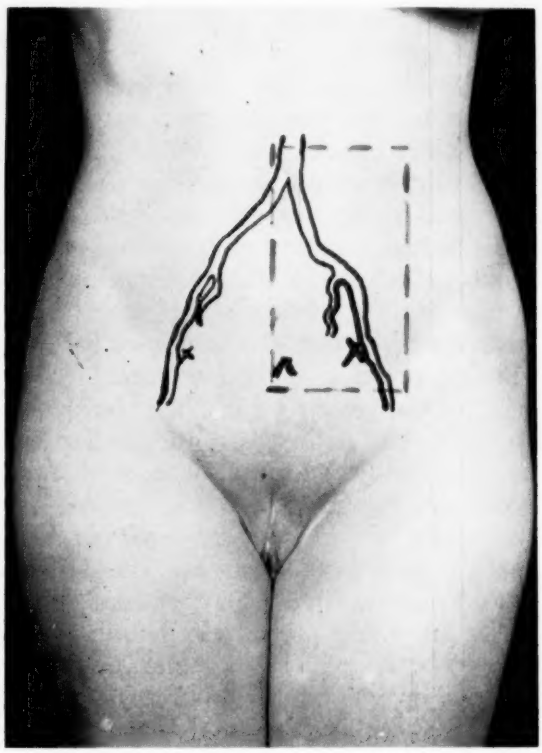

Fig. 3. The location of the uterine canal and major blood vessels drawn on the abdomen of a patient with cancer of the cervix. The crosses represent the location of the obturator lymph nodes, those most frequently involved by metastatic cancer. The inverted V is the projection of the tandem in the cervical canal. The dotted rectangle is a suggested roentgen therapy field which would include cervix, parametria, and all the principal primary and secondary lymph nodes draining the cervix.

side of this, usually lateral to it, one may find lymph nodes which are usually small. We believe that these can be primarily involved when extension of disease is along the uterosacral lymphatics.

In contrast to much of the literature, we have not been able to distinguish grossly enlarged lymph nodes corresponding to the "parametrial" or "ureteral" lymph nodes. We often find direct extension, however, into the parametria, in fact, about twice as frequently as we encounter metastases in lymph nodes. In a series of 91 patients treated by radical hysterectomy, 43 showed direct parametrial spread of tumor and only 15 metastases in lymph nodes. The four groups of lymph nodes can be removed surgically and, as evidenced by an occasional case, cure or prolonged surival may result even when metastatic disease is present. We believe, on the other hand, that

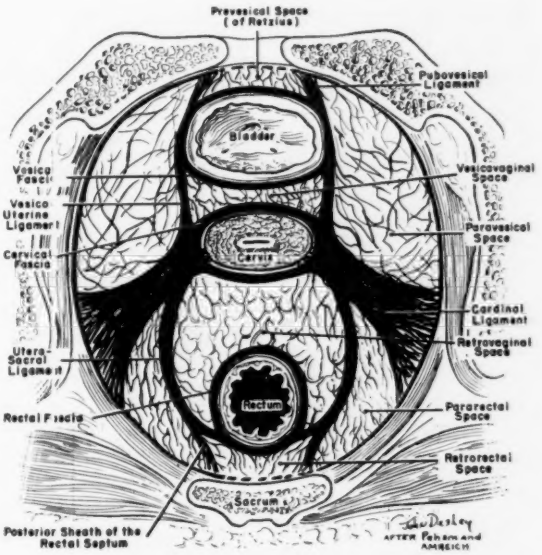

FIG. 5. The fascial planes and spaces of the female pelvis as illustrated by Peham and Amreich. Exenteration is performed easily by blunt dissection of the retrorectal and paravesical spaces, leaving the principal blood vessels in a pedicle which includes cardinal ligament, pararectal space, and uterosacral ligament.

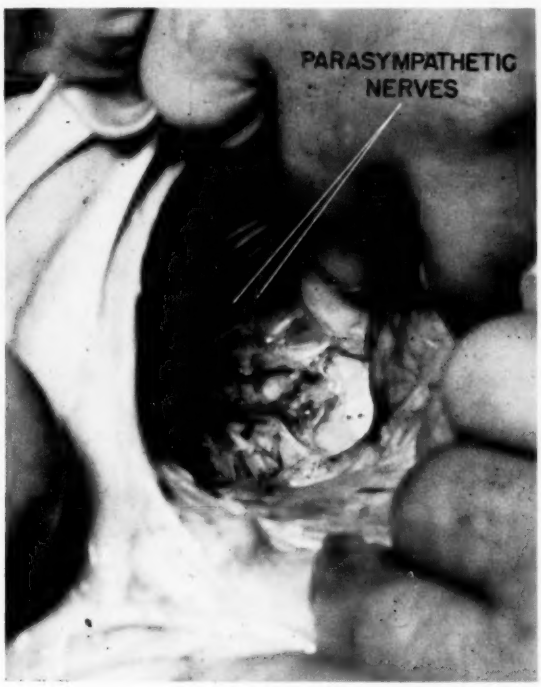

FIG. 4. Dissection of the retrorectal space to show the parasympathetic nerves, nervi erigentes. The promontory of the sacrum lies to the left. The pelvic viscera are being drawn forward to show the hollow of the sacrum and its blood vessels. The parasympathetic nerves are marked.

removal of lymph nodes above the iliac bifurcations is probably useless.

Nerve Supply of the Cervix and Bladder. The frequent temporary paralysis of the bladder which follows radical surgery is distressing both to the operating surgeon and the patient. It constitutes the most frequent cause of prolonged hospitalization. It is so common, in fact, that it inspired us to learn over again something of what was known about bladder innervation, and then to dissect both preserved cadavers in the Department of Anatomy and fresh bodies in the City Morgue to determine just where these nerves ran, how they could be surgically exposed during an operation, and therefore how they could be avoided.[7]

The sympathetic fibers to the pelvic viscera are mainly the familiar presacral nerves. These delicate strands cross over the bifurcation of the aorta and the common iliac arteries. They are easily seen and exposed, as the experienced gynecologic surgeon knows, by cutting the base of the mesosigmoid and bluntly dissecting the

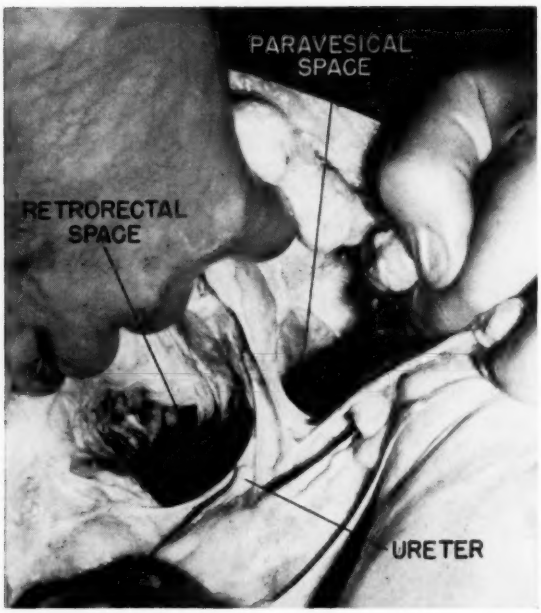

Fig. 6. Dissection of the avascular spaces of the female pelvis. The hollow of the sacrum lies to the left. The left hand retracts the rectum, uterus, vagina and bladder upward to the left, three fingers being in the retrorectal space. The fingers of the right hand dip over the external iliac vessels into the paravesical space. The levator fasciae can be seen at the bottom of this space. The right ureter has been cut. The bridge of tissue is the cardinal and the uterosacral ligament together, with a potential pararectal space between them. This pedicle contains all the branches of the hypogastric artery and vein which supply the pelvic viscera (except for the branches of the pudendal vessels).

peritoneum away from the sacral promontory, thus exposing all the retroperitoneal areolar tissue between the common iliac arteries from the aorta to the sacral promontory.

Below this point, these fibers divide into two main bundles, the right and left hypogastric plexuses, and descend deep into the pelvis in the bases of the uterosacral ligaments. They are joined at the level of the second, third and fourth sacral nerves by two other groups of fibers, the connections from the sympathetic chains which have entered the pelvis lateral to the promontory on each side, and the parasympathetic fibers or nervi erigentes from the second and third and fourth sacral nerves. These nerves can be seen quite easily if one opens the retrorectal space in the hollow of the sacrum by blunt dissection. The pararectal space lies between the nerve plexuses and the vessels in the cardinal ligaments. Anterior to the pararectal space the nerves and the vessels interdigitate.

The presacral nerves can be cut and large segments of them can be destroyed without causing any troublesome loss in function. There seems to be good evidence that these nerves carry pain sensation from the cervix and uterus, and it has been claimed that their complete removal will be followed by painless labor.

The parasympathetic fibers, on the other hand, carry both sensory and motor fibers. When they are cut, the bladder is paralyzed and the patient can no longer distinguish heat from cold in bladder irrigations. The bladder, however, carries its own intrinsic ganglia and nerve net, so that, if overdistention is prevented, automatic contraction can be invoked by straining and control obtained by the voluntary or external sphincter which is innervated by the internal pudendal nerve.

In the usual radical hysterectomy, the parasympathetic fibers are not all cut. They lie deeper than the line of excision which would normally hit the vagina at the junction of its middle and upper thirds. The trauma to these fibers or the ganglia of Frankenhauser's plexus is sufficient to cause high residual urines for ten days to three weeks but no permanent paralysis. If, however, the entire "web" is removed down to the levator ani, as is advocated by Meigs, complete denervation of the bladder ensues. Meigs[5] notes that patients on whom he has operated have had no bladder sensation in over four years, an observation which suggests that the accessory fibers described by McCrea and Kimmel,[4] lying beneath the fascia and along the vessels, either are inconstant or do not carry sensory nerves, and secondly, that the parasympathetic fibers do not regenerate.

One becomes concerned, when doing radical hysterectomy, with the limits one

should observe. Complete removal of the "web" is certainly a more radical procedure than taking only the top half of it between the cervix and the obturator and hypogastric lymph nodes. It results in bladder paralysis. Meigs' patients go home with an indwelling catheter which they retain for two months or more. However, we doubt that such completeness is logical in an operation which preserves the ureters and bladder base, both in close contact with the cancer.

The question of how far to go in lymph node and intervening tissue removal reminds one of the original work of Halsted on the breast. His supraclavicular lymph node dissection has been rejected by most thoughtful surgeons as being not worth the effort and the morbidity.

Blood Vessels of the Pelvic Viscera. Until the revival of radical surgery, the gynecologist was hardly aware of the major pelvic vessels, the external and internal (hypogastric) arteries and veins, but since the major lymph nodes are wrapped around these structures, anyone who dissects out these lymph nodes must become very familiar with them. Rather than reiterate the anatomic details which are found in textbooks, we wish to make a few observations which we have found to be of great importance to the surgeon.

First and foremost is the fact proved by several disastrous accidents of colleagues that ligation or injury and thrombosis of the external iliac artery results in gangrene of the leg. A wound of the external iliac must be repaired or replaced by a graft. The veins, on the other hand, can be sacrificed with impunity. Only transient swelling of the leg, if even that, results. Both hypogastric arteries can be ligated with no disagreeable effect. Ligation of the main hypogastric vein in our hands has resulted in tremendous congestion of all tributary veins and very troublesome and often dangerous bleeding. We avoid such ligation if we possibly can. A common danger in dissecting the lymph nodes is too vigorous retraction of the external iliac vein with the vein retractor which may produce a tear of the wall of the hypogastric vein or of the middle iliac vein (an inconstant vessel present in 23 per cent of all women).[3] Hemorrhage from the hypogastric vein is so profuse as to be frightening. It is controlled first by local pressure and then permanent sutures. The common iliac, external iliac, and hypogastric veins on all sides of such a tear can be tied without stopping the bleeding, a plentiful supply of blood entering from the back through the gluteal veins. Occasionally, one must leave clamps on such a tear for 72 hours to avoid further manipulation which may increase its size and produce truly uncontrollable hemorrhage. We do not believe in packing to control major bleeding if it can be avoided.

In performing exenteration, an almost bloodless procedure can be attained in the following fashion: The ovarian vessels are cut by ligating and cutting the infundibulopelvic ligaments above the brim of the pelvis. The paravesical space is entered far out at the lateral wall of the pelvis and the hand swept around through the space of Retzius down to the fascia over the levator ani muscles. Sometimes a branch of the obturator vein may be encountered in this procedure, but it is easily clamped and tied. The retrorectal space is entered then from an incision in the base of the mesosigmoid and freed down to the anal sphincter. This is done with a hand in the hollow of the sacrum and is a maneuver familiar to the rectal surgeon who is doing abdominoperineal resections of the rectum. The sigmoid and mesosigmoid are cut and the superior hemorrhoidal artery and its branches ligated. This leaves the pelvic viscera attached by their extensions through the levator ani and by two pedicles, one on either side of the pelvis at 4 o'clock and 8 o'clock. These pedicles consist of the uterosacral and cardinal ligaments. In their tops are the ureters.

At this stage, one carries out pelvic lymph node dissection on each side of the pelvis. The ureters are cut and reflected

upward toward the brim of the pelvis. The arteries and veins supplying the pelvic viscera can now be clamped, cut, and ligated all the way down to the pelvic floor, the fascia over the levator ani, without danger and without appreciable blood loss. This procedure leaves intact the branches of the hypogastric artery and vein which go to or come from the legs, buttocks, and perineum. Only the visceral branches are interrupted.

The uretero-intestinal anastomosis and perineal excision of the pelvic viscera are carried out as described by other authors, notably Bricker.[1]

SUMMARY

1. The revival of radical surgery as a method of treating cancer of the cervix has focused our attention anew on the anatomy of the pelvis.

2. With the patient in the supine position, the cervix usually lies above the pubic symphysis and the important parametrial structures and tributary lymph nodes extend upward from there to the umbilicus or above. External roentgen therapy, as usually given, is directed too low and too far laterally.

3. The uterine canal lies at right angles to the axis of the vagina. Adequate radiation therapy is a three dimensional rather than a two dimensional problem.

4. The primary sites of metastases from cancer of the cervix are the obturator, iliac, hypogastric and sacral lymph nodes, the obturator lymph nodes which lie in the obturator fossa (not the obturator foramen or canal) being most frequently involved. These lymph nodes can be removed with occasional success by the surgeon. The secondary lymph nodes around the common iliac arteries and the bifurcation of the aorta, however, probably cannot be removed and are the province, therefore, of the radiotherapist.

5. The nerves to the pelvis run in planes which for want of a better term we have designated uterosacral ligaments. These are below the folds usually so designated by the gynecologist. Cutting the sympathetic fibers seems to do little functional damage. Cutting the parasympathetic fibers (nervi erigentes) paralyzes and denervates the bladder. These fibers are usually not cut completely because they lie so low in the pelvis.

6. Exenteration can be done with little blood loss if the natural compartments of the pelvis are understood and if the vessel containing structures are isolated before they are cut.

New York University
Bellevue Medical Center
New York, New York

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VOL. 77, NO. 5

DOSE DISTRIBUTION AND RESULTS IN CARCINOMA OF THE CERVIX*

A COMPARISON OF CONVENTIONAL HIGH VOLTAGE THERAPY INCLUDING VAGINAL CONE THERAPY WITH SUPERVOLTAGE THERAPY

By RUTH J. GUTTMANN, M.D.
NEW YORK, NEW YORK

VARIOUS methods have been employed in the past in the treatment of carcinoma of the uterine cervix by irradiation. As I had had the opportunity of seeing in use three different techniques during my association with the Memorial Center for Cancer and Allied Diseases and the Francis Delafield Hospital, both in New York City, during the past fourteen years, I thought that an evaluation of the results obtained in patients treated with these techniques would be most interesting and valuable. The workup of this patient material was furthermore facilitated by the fact that the extent of the disease had been classified in both hospitals according to the same principles, since Dr. Howard Taylor, the present Director of the Gynecological Service of the Medical Center, New York, of which the Francis Delafield Hospital is a part, was in charge of the Gynecological Department of the Memorial Center for Cancer and Allied Diseases while these techniques were used.

Three hundred and ninety-three unselected patients with histologically proved carcinoma of the uterine cervix are presented. They are divided into three groups according to the methods employed. The first group was treated by 250 kv. external irradiation, intravaginal cone therapy and radium, the second by 2 mv. external irradiation and radium, and the third by 2 mv. roentgen or cobalt 60 irradiation exclusively.

The group of patients treated with the first method is the largest and has the longest follow-up, namely twelve years. It consists of 301 patients who were treated between 1943 and 1947 in the Radiotherapy Department of the Memorial Center, when the late Dr. Alfred Hocker and, subsequently, I were in charge. Of the 301 patients in this group, 296 had epidermoid carcinoma and 5 had adenocarcinoma.

The second and third groups include 92 patients treated between 1951 and 1955 at the Francis Delafield Hospital, with 2 mv. roentgen irradiation and intracavitary radium for Stages I and II, and supervoltage irradiation, using either a 2 mv. roentgen apparatus or a cobalt 60 teletherapy unit exclusively, for Stages III and IV. Of these patients 89 had epidermoid carcinoma and 3 adenocarcinoma. Forty belonged in the second group and 52 in the third group. Since only a few of them could be followed for five years, they are not considered in the evaluation of survival rates.

Apart from end results the data of interest are alike in the three groups and they will be discussed in the following order: (1) physical factors, including dosage and dose distribution; (2) tolerance to therapy; (3) complications, their incidence, time of occurrence, duration and predisposing diseases; (4) results; and (5) findings in cervix, uterus and lymph nodes at the time of some postradiation surgery.

FIRST GROUP

The 301 patients of the first group who received a combination of conventional external roentgen therapy, vaginal cone therapy, and radium were not treated absolutely identically. In the beginning, smaller dosage and lower voltage were used for vaginal cone therapy than in later years;

* From the Francis Delafield Hospital, Columbia University, New York, New York. Presented at the Thirty-eighth Annual Meeting of the American Radium Society, Houston, Texas, April 9-11, 1956.

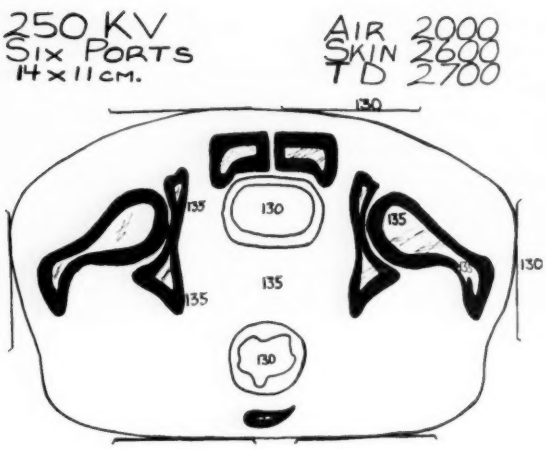

FIG. 1. Treatment approach in conventional external roentgen therapy through six pelvic portals.

however, the general plan and approach remained the same. The method has been described previously in various papers by Taylor, Twombly, and their co-authors, who also evaluated the first 113 patients of this series two years after completion of therapy, and investigated subsequently the complications which had developed. These 113 patients now being ten to twelve years after irradiation are included as part of the entire patient material available for this study. Excluded are all patients who did not finish their course of treatment, those who had been treated with radium needles before intravaginal roentgen therapy, and patients who had only a few cone treatments directed to the cervix prior to surgery.

Physical Factors. The treatment approach in conventional external roentgen therapy was through six pelvic fields; two pairs of opposing anterior and posterior fields combined with one pair of lateral fields to increase the dose to the lateral pelvic walls. In very small patients, occasionally only two anteroposterior fields instead of four were necessary, but approximately the same dose could still be reached. The physical factors were: 250 kv., 70 cm. target skin distance and 2 mm. of Cu half-value layer. In this manner we delivered a daily tumor dose of 250 r through the opposing fields (Fig. 1). The total tumor dose delivered throughout the pelvis was 2,700 r, and this dose was supplemented by the use of vaginal cone therapy to the cervix and both parametria.

During the years of 1943 and 1944 vaginal cone therapy was given in all instances with the 130 kv. unit, a target skin distance of 30 cm. and a half-value layer of 4.2 mm. of Al, while afterwards only Stage I and early Stage II lesions were treated in this manner. Beginning in 1945 advanced Stage II, Stages III and IV lesions received vaginal cone therapy with the 250 kv. machine at a target skin distance of 55 cm. and with a half-value layer of 2 mm. of Cu. The dose with low voltage was 2,000 r to the cervix and 3,000 r to each of the parametria, measured in air. It was increased to 4,500 r measured in air to each of the three fields when high voltage was used. The dose which is added through vaginal cone therapy at 5 cm. depth is illustrated in Table I. The combined total dosage from external roentgen therapy and intravaginal cone therapy at different levels is shown in Table II.

The total treatment time for combined

TABLE I

EXTERNAL ROENTGEN THERAPY AND 130 KV. VAGINAL CONE THERAPY

Contribution from external irradiation	2,700 r
Contribution from intravaginal cone therapy to parametrium and lymph nodes	1,140 r at 5 cm. depth
Total dose	3,840 r

EXTERNAL ROENTGEN THERAPY AND 250 KV. VAGINAL CONE THERAPY

Contribution from external irradiation	2,700 r
Contribution from intravaginal cone therapy to parametrium and lymph nodes	2,250 r at 5 cm. depth
Total dose	4,950 r

Table II

TOTAL DOSE FROM COMBINED EXTERNAL ROENTGEN THERAPY AND VAGINAL CONE THERAPY

	At Surface	At 2 cm.	At 5 cm.	At 8 cm.
Midline dose for a 3.5 cm. vaginal cone, 130 kv., target skin distance 30 cm., half-value layer 4.2 mm. Al				
Cervix	2,000 r	1,400 r	760 r	400 r
Right parametrium and lymph nodes	3,000 r	2,100 r	1,140 r	600 r
Left parametrium and lymph nodes	3,000 r	2,100 r	1,140 r	600 r
Midline dose for a 3.5 cm. vaginal cone, 250 kv., target skin distance 55 cm., half-value layer 2.2 mm. Cu				
Cervix	4,500 r	3,600 r	2,250 r	1,350 r
Right parametrium and lymph nodes	4,500 r	3,600 r	2,250 r	1,350 r
Left parametrium and lymph nodes	4,500 r	3,600 r	2,250 r	1,350 r

The fall-off on the margins of the field was 75% with low voltage and 66% with high voltage. The dosage therefore was not a homogeneous one.

external irradiation and intravaginal cone therapy was five to six weeks, while the radium dose of 6,000 gamma roentgens delivered to the cervix directly with a tandem was given in one application three weeks after completion of roentgen therapy. It is of great importance in vaginal cone therapy to have the same operator attend the patient each time in order to guarantee the same position of the cone. The setup may be a time consuming procedure when done well and properly, but the results justify the effort.

Tolerance. The immediate reactions to irradiation were usually a moderate amount of nausea, vomiting, and diarrhea. The question has been raised whether the diarrhea was increased by the use of vaginal cone therapy. In my opinion, this treatment does not increase diarrhea or other rectal complaints when the cone is inserted in the horizontal position, pointing toward the sacral promontory and away from the rectum.

Complications. Late complications, which occurred only very rarely before the end of the first year following treatment, became manifest in 54 patients; there were cystitis in 28, proctitis in 20 and fistulae in 6 women. Fistulae which had been present before treatment were obviously not included in the evaluation of complications after therapy. Table III shows the distribution of late complications in the various stages.

The general duration of bladder and rectal symptoms was two to three months. Two patients, however, suffered off and on from bladder symptoms for two to three years, and 2 others had occasional bleeding from the rectum for an equal period. Five of the patients who developed intestinal complications had a history of diverticulosis and diverticulitis or colitis, which may be considered as a predisposing disease.

The use of low or high voltage roentgen rays in vaginal cone therapy had no influence on the incidence of complications as indicated by the surprisingly similar figures shown in Table IV.

The absence of complications in Stage IV patients is easily explained by the short

Table III

DISTRIBUTION OF LATE COMPLICATIONS IN VARIOUS STAGES

	Cystitis	Proctitis	Fistulae
Stage I	9	9	0
Stage II	14	6	5
Stage III	5	5	1
Stage IV			

TABLE IV

CORRELATION OF RATES OF COMPLICATIONS WITH LOW AND HIGH VOLTAGE VAGINAL CONE THERAPY

	Total No. of Complications	Total No. of Patients Treated with Low Voltage	Complications with Low Voltage	Total No. of Patients Treated with High Voltage	Complications with High Voltage
Stage I	18	64	17 = 28.1%	0	0
Stage II	25	107	20 = 18.5%	22	5 = 23%
Stage III	11	40	5 = 12.5%	53	6 = 11.1%
Stage IV	0	7	0	8	0

life span after completion of therapy in that group.

Results. The survival times are shown in the following tables; five year survival of patients with Stage I, II, III, and IV lesions are illustrated in Tables V through VIII. Longer survivals are accounted for in Tables IX through XI.

TABLE V

FIVE YEAR SURVIVAL

Stage I

		Alive	Dead	Cause of Death	
				Disease	Other Cause
Number of patients	64	57	7	6	1
Treated with low voltage vaginal cone therapy and external roentgen therapy	64	57 89.1%	7		
Treated with high voltage vaginal cone therapy and external roentgen therapy	0				

TABLE VI

FIVE YEAR SURVIVAL

Stage II

		Alive	Dead	Cause of Death	
				Disease	Other Cause
Number of patients	129	92 71.3%	37	37	
Treated with low voltage vaginal cone therapy and external roentgen therapy	107	75 70.1%	32		
Treated with high voltage vaginal cone therapy and external roentgen therapy	22	17 77.3%	5		

Two other patients not included in this group had a Wertheim operation six to twelve months after radiation therapy and no evidence of disease was found.

TABLE VII

FIVE YEAR SURVIVAL

Stage III

		Alive	Dead	Cause of Death	
				Disease	Other Cause
Number of patients	93	20 *21.3%*	73	69	heart attack 2 pneumonia 1 one day postoperatively 1
Treated with low voltage vaginal cone therapy and external roentgen therapy	40	6 *15%*	34		
Treated with high voltage vaginal cone therapy and external roentgen therapy	53	14 *26.4%*	39		

Two patients had lymph node dissections, one three months, the other five years, after radiation therapy, and no evidence of disease was found in either.

TABLE VIII

FIVE YEAR SURVIVAL

Stage IV

		Alive	Dead	Cause of Death	
				Disease	Other Cause
Number of patients	15	1 *6.6%*	14	13	cerebral hemorrhage 1
Treated with low voltage vaginal cone therapy and external roentgen therapy	7	0	7		
Treated with high voltage vaginal cone therapy and external roentgen therapy	8	1 *12.5%*	7		

TABLE IX

MORE THAN FIVE YEAR SURVIVAL

Stage I

Number of Patients	Alive without Evidence of Disease	Average Survival Time	Lost for Follow-up	Dead after Five Years
57	49 = 86%	over 11.5 yr.	4	4 *Cause of death* disease 2 lung metastases 1 second primary ? second primary proved 1

One patient of this group had a Wertheim operation more than five years after irradiation, because it was believed that she had active disease again. However, the surgical specimen was free of disease.

TABLE X

MORE THAN FIVE YEAR SURVIVAL

Stage II

Number of Patients	Alive without Evidence of Disease	Average Survival Time	Lost for Follow-up	Dead after Five Years
92	76 = 82.6%	over 8.8 yr.	5	11 *Cause of death* disease 4 second primary 1 cerebral hemorrhage 3 coronary 1 intestinal obstruction 1 accident 1

One patient of this group had a Wertheim operation more than five years after irradiation, because it was believed that she had active disease again. However, the surgical specimen was free of disease.

The over-all five year survival rate in the present material is 56.5 per cent. This figure, when compared with the survival rate in the different stages, raises anew the question whether the clinical classification as a method is exact enough to allow detailed comparative studies of statistics from various centers.

A very interesting case history of a patient with a Stage III lesion is reported. The patient was an eighteen year old girl who finished her course of radiation therapy on August 6 and underwent a laparotomy on September 12 of the same year. At the time of the operation, multiple biopsies were taken which were all positive and the patient was considered inoperable. Subsequently, the usual radium treatment was given. Today, ten years later she is alive and without evidence of disease. There can be no doubt that her survival would have been credited to surgery had radical surgery been performed at the time of the exploratory laparotomy. The result in this patient is a good proof that time is needed after radiation therapy to assure its full effect.

Table XII shows a comparison of end results after the use of low and high voltage vaginal cone therapy. Evaluation is possible only in Stages II and III; Stage I was treated solely by low voltage cone therapy and in Stage IV was only one surviving patient.

Another interesting item is the comparison of survival rates among the various age

TABLE XI

MORE THAN FIVE YEAR SURVIVAL

Stages III and IV

	Number of Patients	Alive without Evidence of Disease	Average Survival Time	Lost for Follow-up	Dead after Five Years
Stage III	20	18 = 90%	over 8.7 yr.	1	1 *Cause of death* disease 1
Stage IV	1	1 = 100%	8 yr.		

TABLE XII

CORRELATION OF RATE OF SURVIVAL WITH LOW AND HIGH VOLTAGE VAGINAL CONE THERAPY

Five Year Survival

	Stage II	Stage III
Low Voltage Vaginal Cone Therapy	70.1%	15%
High Voltage Vaginal Cone Therapy	77.3%	26.4%

High voltage vaginal cone therapy gave better results. The improvement was over 10% in Stage II and 76% in Stage III.

groups as shown in Tables XIII and XIV. The figures indicate that the five year survival is certainly not worse in the younger age group despite the often claimed greater malignancy index of a lesion in young people.

SECOND GROUP

STAGES I AND II

The second group consists of 40 patients treated at the Francis Delafield Hospital by a combination of intracavitary radium and external 2 mv. roentgen irradiation, as mentioned previously.

Physical Factors. It is our policy to start with the radium treatment and have it followed by the external irradiation. We give a dose of 8,000 gamma roentgens to Point A, approximately one third of which reaches Point B. Point A is defined as 2 cm. cephalad from the external os and 2 cm. lateral from it, while Point B is at

TABLE XIII

COMPARISON OF SURVIVAL RATES AMONG VARIOUS AGE GROUPS

Stage I and II

Age Group	No. of Patients	Alive	Dead	Lost for Follow-up
25–30	3	2=67%	1	
30–40	38	31=81.6%	7	
40–50	56	47=83.9%	9	1
50–60	60	46=76.7%	14	
60–75	35	23=65.7%	12	

TABLE XIV

COMPARISON OF SURVIVAL RATES AMONG VARIOUS AGE GROUPS

Stage III

Age Group	No. of Patients	Alive	Dead	Lost for Follow-up
18–30	3	2=67%	1	
30–40	14	3=21%	11	
40–50	26	3=11.5%	23	
50–60	21	3=14.3%	18	
60–70	29	9=31%	20	

the same level but 3 cm. further laterally. We are using Manchester ovoids or the Corscaden applicator and are applying the radium in two sittings. The course of external irradiation begins ten days after completion of the radium therapy. A uniform dose of 5,000 r is administered throughout the pelvis with the 2 mv. roentgen unit at a target skin distance of 100 cm. and with a half-value layer of 6.8 mm. of lead. A daily tumor dose of 200 r is given; the course of treatment lasts about five weeks (Fig. 2). The entire treatment time for radium and external irradiation combined is about eight weeks.

When this program was started treatment was given through two opposing 15

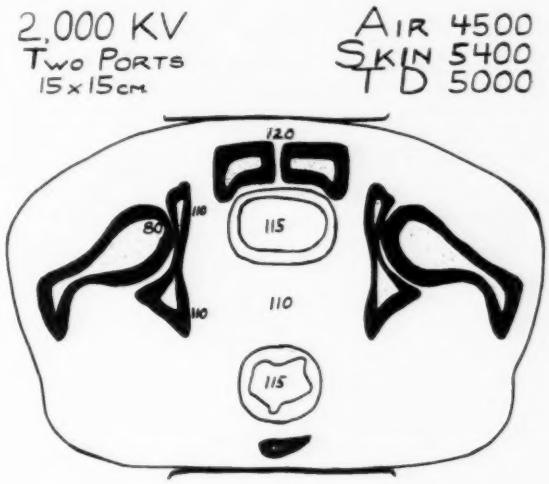

FIG. 2. Treatment approach in 2 mv. roentgen therapy through two pelvic portals.

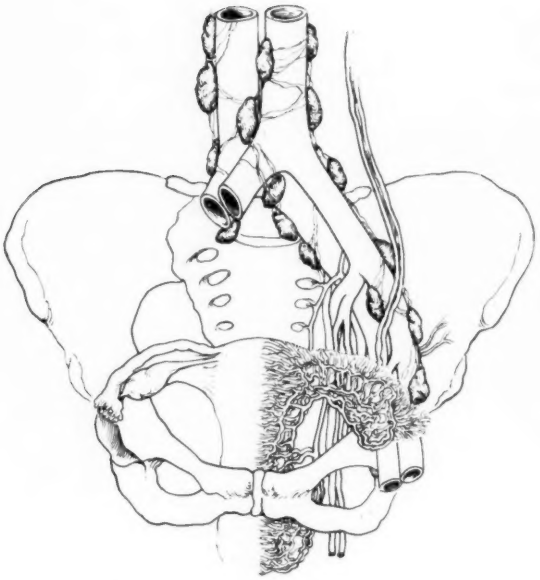

Fig. 3. Lymphatics of the pelvis

by 15 cm. pelvic fields with a 3 cm. lead-strip in the center for protection of bladder and rectum. I abandoned the leadshield without ill effects, after persistent disease was found in the cervix of 2 patients, and after it became obvious to me that too many lymphatics which needed irradiation did not receive it. Figure 3 demonstrates the lymphatics. Figure 4 shows the field of irradiation with a central leadshield. When the leadshield is used, the central lymphatics are deprived of a sufficient dose (Fig. 5).

What do we want to include in the field of irradiation? The answer is cervix and corpus uteri, vagina and parametria, and as much of the lymphatics and lymph nodes as possible. At the present time we extend the fields to the lower lateral aortic lymph nodes in order to include them, even if it means enlarging the treated area to 17 by 15 cm.

In order to be certain that all the vital points are within the field, the patients are examined vaginally in the actual treatment position, that is, on the treatment table. The lower border of the field is outlined after the site of the cervix has been established. It is always amazing to realize that there may be a difference of 3 to 5 cm. in the location of the pelvic organs in a patient in the proper treatment position and one in stirrups. Before starting the treatment proper, a localization film is taken on the 2 mv. roentgen unit with the patient on the treatment table and in the treat-

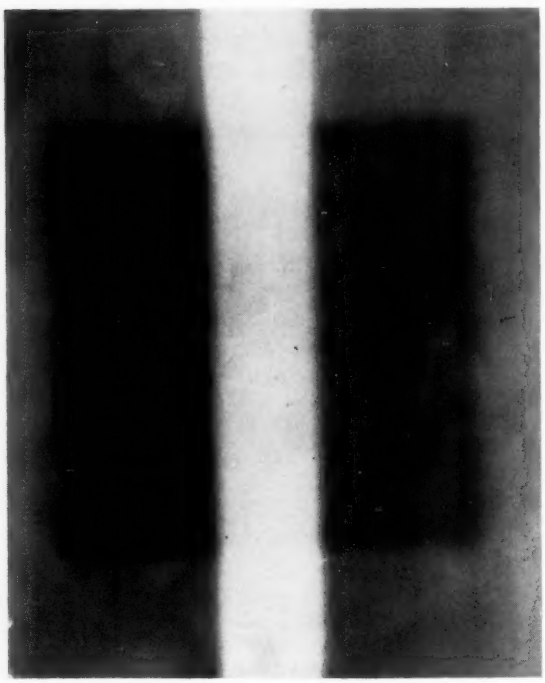

Fig. 4. Field of irradiation with a central leadshield.

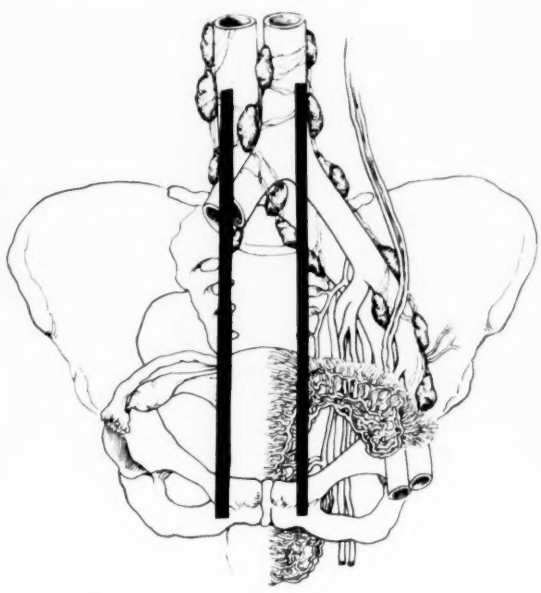

Fig. 5. Diagram of pelvis with central leadshield superimposed.

ment position. Figure 6 shows the localization film which outlines the field of irradiation as described before.

Tolerance. The tolerance to a daily tumor dose of 200 r is good, there is no nausea or vomiting. Some of the patients start to complain of diarrhea around the third week of their treatment, but it has been possible to control this discomfort with simple methods. There has not been one instance of bloody diarrhea or bloody mucus, and it has never been necessary to interrupt therapy. Bladder irritation during treatment is extremely rare.

The total tumor dose of 5,000 r is delivered with a skin dose of 5,400 r; no moist desquamation has occurred.

Results, Complications and Postradiation Operative Findings. Figures about end results in this patient material will not be given. There has not been as yet a five year follow-up, and preliminary reports are unreliable. Otherwise, our experience concerning this group can be summarized as follows:

There were 12 patients with carcinoma of the cervix Stage I. Their immediate tolerance to therapy was excellent, and no late complications, fibrosis and late skin changes included, have occurred. In 3 of these patients lymph node dissections were done three to six months after completion of irradiation and not one of the cases showed any evidence of disease in the nodes.

Twenty-eight patients were treated for carcinoma of the cervix, Stage II. Eleven of these patients had undergone, previously, some kind of treatment and only the remaining 17 will lend themselves to a future evaluation of this method. The immediate tolerance to irradiation was as good as in patients with carcinoma Stage I, but late complications occurred on three occasions. One patient, a diabetic, developed cystitis of four weeks' duration three months after completion of irradiation, although she had been treated with a central leadstrip. One patient suffered from proctitis, which had started two months after therapy, for one month. A third patient developed a rectovaginal fistula twelve months after completion of therapy. This patient had been afflicted with diverticulosis and diverticulitis of the lower intestinal tract for many years and had complained of rectal symptoms throughout the course of treatment. She became asymptomatic following a colostomy, which is to be closed in the near future. Lymph node dissections were performed on 10 patients with carcinoma of the cervix, Stage II, three to six months after completion of treatment. Nine patients were free of disease and 1 patient had a single positive lymph node in the right obturator area among eight other lymph nodes which were negative, as were the lymph nodes on the opposite side.

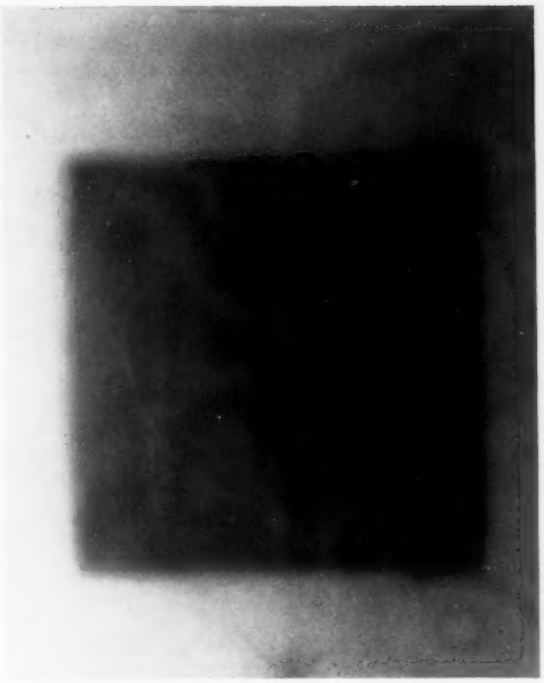

Fig. 6. Localization film outlining the field of irradiation with the 2 mv. roentgen unit.

THIRD GROUP

STAGES III AND IV

The third group comprises 52 patients. We have treated with our method of supervoltage irradiation, either with 2 mv. roentgen rays or with cobalt 60, 31 patients with Stage III and 21 with Stage IV car-

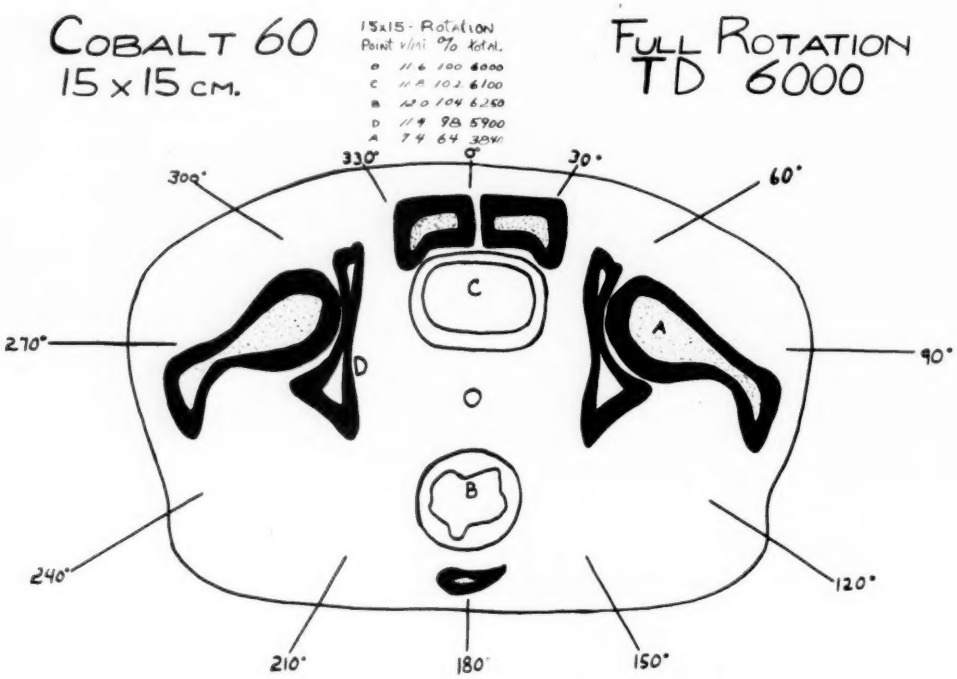

FIG. 7. Treatment approach in cobalt 60 teletherapy using full rotation.

cinoma of the cervix, but half of the group already had had some kind of treatment previously.*

Physical Factors. Our aim in this group is to deliver a tumor dose of 6,000—7,000 r, which is given as a daily tumor dose of 200 r throughout the pelvis during six to seven weeks. In the beginning these patients were treated with the 2 mv. roentgen unit through two opposing 15 by 15 cm. fields. For the past two years, the cobalt 60 unit has been used, and the same dose has been given through a 15 by 15 cm. portal with full rotation in order to get an even distribution throughout the pelvis (Fig. 7, cross-section and plan). A 17 by 15 cm. field has been used when necessary.

Tolerance. The general tolerance is the same as described above in the use of supervoltage irradiation in Stage I and II lesions.

Results, Complications and Postradiation Operative Findings. The rate of survival after one year in patients with carcinoma of the cervix Stage III merits special mention, since it has been definitely better in this group than in our patients treated with conventional therapy.

Late complications occurred only once among the Stage III patients. This was a case of cystitis of one month's duration which started three years after therapy.

Two vesicovaginal fistulae were noted in Stage IV patients. One occurred two months after completion of therapy, shortly before the patient died from generalized disease. The second fistula developed four years ago during therapy in a patient who is still alive without evidence of disease, and who does not feel disturbed in any way by the still present fistula.

Lymph node dissections were performed in 4 patients. The lymph nodes were negative in three instances, positive in one. The history of one of the patients with negative lymph nodes may be of interest. This patient had an exploratory laparotomy in July, 1952, before radiation therapy, at which time a salpingo-oophorectomy and excision of one of the enlarged iliac lymph nodes were done, but dissection of the parametria was not possible. The pathology

* The treatment policy in patients with cancer of the cervix—Stage III—has been changed in the meantime. The external cobalt 60 therapy is now supplemented by intracavitary radium treatment.

report stated that the lymph node was entirely replaced by neoplastic tissue. Eight months after radiation therapy the patient had a lymph node dissection. A thorough examination of all the lymph nodes and many biopsies taken from various areas revealed fibrosis but no evidence of disease. The patient is alive three and one-half years after radiation therapy.

SUMMARY

Three hundred and ninety-three unselected patients, who had been treated by three different methods of irradiation for proved cancer of the uterine cervix of various stages since 1943, have been critically evaluated. Although it was not possible to compare the end results for reasons explained, certain factors like tolerance and complications lend themselves for analysis. This study attempts to bring out the potentialities and limitations of each method.

Between 1943 and 1947, 301 patients have been treated with conventional therapy, external roentgen irradiation, vaginal cone therapy and radium with a five year survival rate of 89.1 per cent in Stage I, 71.3 per cent in Stage II and 21.3 per cent in Stage III lesions. The last figure was raised to 26.9 per cent for the group of patients who received high voltage vaginal cone therapy instead of the low voltage cone treatments. The results in Stage IV have been poor. One patient survived for eight years and one patient, who was without clinical evidence of disease, died from hypertension. The over-all five year survival rate is 56.5 per cent.

The dosage with conventional therapy was 2,700 r throughout the pelvis by external roentgen irradiation, a maximum of 2,250 r at 5 cm. depth added from the vaginal cone therapy, and 6,000 gamma roentgens to the cervix proper, contributed by the radium.

The administration of these treatments is time consuming, often uncomfortable for the patient, and complications are not unusual. However, the results are good and in line with the best ones reported for this disease anywhere. In my opinion the method is to be highly recommended when only conventional equipment is available,

In view of these facts the question arises as to what improvement can be hoped for and expected with supervoltage therapy. Foremost is the immediate tolerance which is much better with this type of irradiation, a major point considering the importance of response, resistance and defense mechanism of the host. The general condition of the patient is less impaired by aggressive treatment with supervoltage equipment. This is a contributing factor of utmost significance in the outcome of therapy.

Late complications seem to be less frequent after supervoltage therapy, although the limited elapsed time does not permit definite conclusions.

The possibility of delivering a homogeneous high dosage throughout the entire pelvis carries the potentialities of better control of the disease in some instances of Stage I or Stage II lesions where we had to admit defeat, sometimes after several years, with conventional therapy. The same holds true in Stage III lesions, possibly even to a higher degree, since we were able to demonstrate, already, an increase of the five year survival by 76 per cent with the use of 250 kv. vaginal cone therapy as compared with 130 kv. cone therapy.

CONCLUSION

Comparison of high voltage and supervoltage irradiation in the treatment of carcinoma of the uterine cervix shows that certain qualities of the supervoltage therapy are advantageous for the patient, promising improvement of previous results. Though the nature of the disease is such that we will not be able to increase the five year survival rates to 100 per cent with any treatment known, each life saved makes our efforts worthwhile and represents a tremendous step forward.

98–19 64th Avenue
Forest Hills, New York

The author wishes to express her thanks to Dr. James J. Nickson, Chief of the Radiotherapy Department, Memorial Center, New York, for the use of the patient material of the first group treated between 1943 and 1947.

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COBALT 60 THERAPY OF LIP CANCER

WITH BLOCK DISSECTION OF LYMPH NODES*

By J. ERNEST BREED, M.D.,† *and* WALTER W. CARROLL, M.D.†
CHICAGO, ILLINOIS

THE availability of cobalt 60 makes it mandatory to re-examine the various techniques of radium therapy to determine how best to use it. Most of the familiar methods of utilizing radium are predicated upon its scarcity. The technique to be described was devised by Dr. Frank E. Simpson between the years 1917 and 1925. Dr. Simpson had at his sole disposal 1,700 mg. of radium in an emanation plant. The powerful radon tubes obtained from this plant provided a very flexible armamentarium. It was, therefore, unnecessary for him to compromise radiobiologic and surgical principles in the utilization of weak sources as was necessary in many centers.

During the past twenty years 155 patients with lip cancer have been treated by one of us with a small applicator containing from 200 to 500 mc of radon applied to the surface of the growth. Thirty minute treatments are administered daily or on alternate days over a period of three to four weeks. At a distance of 4 to 10 mm. the applicator is placed successively over different sections of the periphery of the growth utilizing the mucous membrane surface, the free border and the skin surface. This technique is nontraumatic, the tumor bed is preserved, the patient is ambulatory and may continue his usual work. The cosmetic result as a rule is excellent.

The lesions considered in this paper were all over 5 mm. in thickness. Small lesions are treated with hard beta rays from radium. These rays are most effective to a depth of about 8 mm. and do not damage the normal tissues beyond this depth.

Paterson[1] has stated that the surface radium applicator "is in many senses the only ideal method (of irradiation) in that, where applicable, it enables radiation to be given without trauma to a zone of tissue almost exactly limited to the tumour-bearing zone (treatment zone)."

The expense of radium or radon prohibits its general use but Co^{60} with comparable gamma rays is a satisfactory substitute. We have 300 mc of cobalt which is contained in an aluminum jacket. The entire applicator measures $2 \times 1 \times 0.5$ cm. in size and has the power of 500 mg. of radium. At a distance of 1 cm. the dose rate is 30 gamma r per minute.

BIOPSY

All suspicious lesions should have microscopic examination. The tumor bed should not be disturbed as opening blood channels may facilitate metastasis. A competent pathologist can recognize cancer cells without the tumor bed.

TECHNIQUE OF COBALT 60 THERAPY

With the patient recumbent, cotton is placed between the lower lip and the mandible to displace the growth as far as possible from the bone. A finger cot stuffed with cotton, when placed between the teeth, provides distance from the upper lip. A gold plate 5 mm. in thickness is strapped on the upper lip for further protection. A wooden block of the desired thickness is strapped over the treatment area and a nurse, standing behind a 2 inch lead slab, quickly applies the cobalt to the wooden block.

The treatment lasts for twenty to thirty minutes and may be repeated daily. The length of the treatment as well as the frequency is adjusted to spread the entire

* Read at the Fifth Inter-American Radiological Congress, April, 1955.
† Departments of Radiology and Surgery, Northwestern University Medical School, Chicago, Illinois.

dose over a period of three to four weeks.

There is no set tumor dose. We plan to deliver from 5,000 to 8,000 gamma r to the tumor, but the amount actually delivered depends upon the observed sensitivity of the tumor and of the surrounding tissues. In treating the patient over a period of three to four weeks not only are the many other advantages of the divided dose technique obtained, but also the sensitivity of the tumor is demonstrated.

LYMPH NODES

Except for an occasional patient, metastatic cancer in lymph nodes cannot be cured by external irradiation. Persistently enlarged lymph nodes should be removed by block dissection but only after the primary tumor is completely controlled. Treatment of the lymph nodes with Co^{60} or radon at 2 cm. distance will stop further growth until destruction of the primary tumor is assured. In fact, considerable shrinkage of the lymph nodes will occur. If the lymph nodes completely disappear or if no new lymph node enlargements appear during irradiation, no further treatment is deemed necessary.

LYMPH NODE DISSECTION

When lymph node metastases occur in lip cancer, the spread is seldom below the level of the omohyoid muscle in the deep jugular chain. The most commonly involved cervical lymph nodes are those found in the submental and submaxillary triangles, either unilateral or bilateral.

Occasionally, the upper (subdigastric) jugular lymph nodes may receive tumor emboli from a well lateralized lesion. It is rare for lip metastases to be found in the deep jugular chain below the level of the omohyoid muscle except in terminal states. For these reasons we believe a bilateral supraomohyoid neck dissection will suffice for the great majority of patients who present lymph node metastases. This procedure easily can be converted to a complete unilateral deep jugular dissection if the upper jugular lymph nodes are found to be involved. Block excisions of this order can be accomplished under either local or endotracheal anesthesia. Average duration of hospitalization approximates five to eight days depending upon the extent of dissection and the patient's particular response.

If the primary lip cancer has been completely controlled, recurrence in the neck has not been a problem unless the mandibular periosteum is invaded by contiguous growth from lymph nodes along the facial artery as it leaves the submaxillary triangle. Complete hemimandibulectomy in continuity with the neck dissection is mandatory under such circumstances because the extent of invasion through the mental foramen and along the bone cannot be accurately determined by the naked eye.[2] Cosmetic and functional results have proved to be very satisfactory in these patients.

TABLE I

CANCER OF LIP

(over 5 mm. in thickness)
Treated with Radon
1933–1951
Three Year Results

Total Cases			155
Indeterminate Group	No.		
Discontinued treatment	9		
Died of intercurrent diseases	7		
Lost to follow-up	15		
			31
Determinate Group			
Died of disease	15	12.1%	
Living with disease	2	1.6%	
Three year clinical cure	107	86.3%	
		100.0%	124
Radon Failures			
Total Cases			17
Local lesion cured (died of metastasis)	5		
Local lesion not cured (7 with massive involvement)	12		
			17

STATISTICS

Table 1 discloses the results of 155 cases treated between 1933 and 1951 with a powerful radon applicator.

In the determinate group of 124 cases, three year clinical cures numbered 107 or 86.3 per cent. Of the 17 cases that died, 5 had local cure but died of metastasis.

SUMMARY

Surgeons and radiologists should work together to give the patient the best possible care. Some local lesions require surgery. Most lip cancers can satisfactorily be treated with a gamma ray source such as radium, radon or cobalt 60. The technique described requires short daily treatments with a radon or cobalt applicator containing the equivalent of from 200 to 500 mc of radon. The procedure is nontraumatic, preserves the tumor bed and permits the patient to be ambulatory.

Persistent lymph nodes should be removed by block dissection. Bilateral supraomohyoid dissection will suffice for the majority of such patients. Additional mandibular resection is often mandatory when the periosteum is invaded secondarily from contiguous lymph node metastases.

J. Ernest Breed, M.D.
The Breed Radium Institute
59 East Madison Street
Chicago 3, Illinois

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CARCINOMA OF THE ESOPHAGUS

A STATISTICAL STUDY

By HAROLD S. PETTIT, M.D.
CHARLESTON, SOUTH CAROLINA

IN RECENT years carcinoma of the esophagus has been attacked with considerable vigor and slightly better results than in the past. This is true for both radiation therapy and surgical therapy. Five year cures for primary epidermoid carcinoma of the esophagus with either method are still limited to an occasional case. For example, Sweet[15] reported 17 cases living five years, but 16 of these were carcinoma of or near the cardia. We cannot help but believe that some of these cases were primary carcinoma of the stomach involving the esophagus secondarily. Only one of his five year survivals had a mid-esophageal lesion. With better understanding of this disease, perhaps a selection of patients could be made in such a way as to increase the cure rate and the degree of palliation.

Carcinoma of the esophagus is unusually prevalent in the Charleston, South Carolina area. During the period from January 1, 1940 to January 1, 1955, 253 cases of carcinoma of the esophagus were seen in the clinics of the Medical College of South Carolina and in Roper Hospital. The comparative incidence is seen in Table I.

This study encompasses a series of 219 patients seen either at the clinics of the Medical College of South Carolina or at Roper Hospital in the eleven year period from 1943 through 1955.

Table II gives the incidence according to the age of the patient and the grade of the tumor. We see no significance in the grade of the tumor, but it was tabulated with the thought that it might be pertinent.

Table III shows the incidence according to race and sex. Our youngest patient was twenty-eight, there being 2 of this age and 1 of twenty-nine, but the average age at the onset of the disease was fifty-eight. In this area the disease affects primarily the poor Negro.

An obvious suspect in the etiology of the disease when considering our patients is the diet. The staples are rice and hominy for most. Unfortunately, chart data are not

TABLE I

COMPARATIVE INCIDENCE OF CARCINOMA OF THE GASTROINTESTINAL TRACT AT ROPER HOSPITAL AND THE MEDICAL COLLEGE OF SOUTH CAROLINA

Site	1940 through 1951	July 1951 through 1954	Total
Esophagus	155	98	253
Stomach	146	68	214
Colon and Rectum	103	89	192

TABLE II

INCIDENCE ACCORDING TO GRADE OF TUMOR AND AGE

Grade	Age 28–30	Age 30–40	Age 40–50	Age 50–60	Age 60–70	Age over 70	Total
I	1	2	5	9	6	4	27
II	1	7	24	27	32	11	102
III	1	2	6	10	8	7	34
IV			2	3	2	1	8
Adenocarcinoma			1			1	2
Not Graded		4	9	11	18	4	46
Total	3	15	47	60	66	28	219

Table III

INCIDENCE IN RELATION TO SEX AND RACE

Sex and Race	Number	Per Cent
Colored Males	107	48.8
Colored Females	71	32.4
White Males	25	11.4
White Females	16	7.3

sufficiently detailed to evaluate accurately the importance of diet, but it is apparent that in 35 per cent the diet was grossly inadequate, containing eggs, meat and milk only occasionally and fruit rarely. Very few were heavy users of tobacco. The tobacco habits were recorded on the charts of 81 patients. Twenty-six used no tobacco in any form. Only 7 chewed tobacco or used snuff. The use of alcohol did not seem to be of any importance. Heredity cannot be evaluated from family histories as they are too inaccurate, but at least there were no siblings in our series. From a review of the charts, one feels most keenly the lack of detailed dietary information and the need for future meticulous questioning and recording of such data. The areas from which the patients have come seem to be about evenly distributed throughout the natural drawing territory of the institution. One hundred and twenty patients lived in Charleston County. Adjoining counties contributed 26 patients. Fifteen patients gave no address. The others came from scattered communities over the state.

TYPES OF TUMOR

There are three main forms of carcinoma of the esophagus: (1) Constricting, napkin ring type, prone to be relatively short; (2) bulky, fungating tumor obstructing the lumen by filling it; and (3) flat ulcerating lesions, rapidly infiltrating the wall longitudinally, or not producing symptoms until there has been marked local extension.

Many of the lesions do not fit into such a rigid classification, but will be predominantly of one type. As the esophagus lacks a serosal wall, infiltration into the surrounding tissues may occur early in any of the forms. The exceedingly rich lymphatic supply permits early extension along the wall and the establishment of metastases in lymph nodes well removed from the primary site. McCort[10] has made an excellent diagram and evaluation of this lymphatic system.

SYMPTOMS

The most common symptom was dysphagia, with secondary loss of weight and general debility. Over 90 per cent gave dysphagia as a presenting complaint. The second most common symptom was pain due to ulceration and infection of the neighboring tissues. The esophagus contains no pain fibers, so it was not until other structures were involved that pain was experienced. Weight loss and anemia were almost invariably present. Although the average duration of symptoms was 5.8 months, the average weight loss was 35 pounds. Only 5 patients reported no weight loss. The greatest reported was 100 pounds in a colored female who had had symptoms for one year. Occasional primary symptoms were hemorrhage (hematemesis or melena), cough due to invasion of the trachea or left main bronchus, hoarseness secondary to paralysis of the recurrent laryngeal nerve, and dyspnea (Table IV).

In the cervical region the maximum duration of symptoms was 48 months and the minimum 1 day. Only 3 had symptoms of less than 3 months' duration.

There were 29 cases of carcinoma of the thoracic esophagus above the arch of the aorta. The average duration of symptoms in this group was only 4.5 months. The maximum duration of symptoms was 12 months, and the minimum was 2 days. Fifteen had symptoms for 3 months or less.

The most common site of the tumor was the mid-thoracic area. There were 121 cases with a maximum duration of symptoms of 36 months, and a minimum of 3 days. Fifty-eight of these patients had

TABLE IV

SYMPTOMS IN RELATION TO LOCATION OF LESION

Location of Lesion	Average Duration of Symptoms	No. of Cases with Symptoms Less Than 3 mo.	Percentage of Cases with Symptoms Less Than 3 mo.	Total No. Patients	Per Cent
Cervical	9 mo.	3	11.1	18	8.8
Upper ¼ Thoracic	4.5 mo.	15	51.7	29	14.2
Middle ½ Thoracic	4.9 mo.	58	47.9	121	60.0
Lower ¼ Thoracic	5 mo.	16	45.6	35	17.0
Total	5.8 mo.	92	45.3	203	100.0

symptoms for less than 3 months. One patient gave a history of dysphagia of 7 years' duration, but he had an aneurysm of the arch of the aorta and he was not included in this average. There were only 35 cases with the primary lesion located in the lower one quarter of the thoracic esophagus, the most favorable region for resection. The maximum duration of symptoms was 20 months, and the minimum 2 days. Sixteen had symptoms for 3 months or less.

In all, 92 patients out of a total of 203 had symptoms for less than 3 months, yet only 47 of these patients had resectable lesions. The duration of symptoms was not a guide as to the resectability of the tumor. Of 42 patients with symptoms for one month or less, only 11 were found to be resectable.

DIAGNOSIS

Almost all patients with carcinoma of the esophagus will have roentgenologically demonstrable lesions. Symptoms do not occur until there is sufficient obstruction or interference with swallowing to alter the esophagus to such a degree that it is not difficult to recognize the presence of a lesion. Occasional lesions may be missed, depending on the skill and care of the examiner. In any patient with dysphagia, the esophagus must be examined in both the upright and supine positions with thin and thick barium. Burgess, Baggenstoss, Moersch and Clagett[2] have reported a false negative percentage of 10 per cent. In our series there was a false negative barium examination of the esophagus in 8 of 200 cases, or 4 per cent. The identification of the lesion is another matter. Carcinoma of the esophagus may be mistaken for benign tumors, varices, benign strictures, diverticula, extrinsic lesions, and peptic ulcers, but at least the need for esophagoscopy is recognized, and the surgeon knows which area in the esophagus is under suspicion. This is important because it gives the surgeon a better chance to establish the diagnosis by esophagoscopy. In at least 4 cases the initial esophagoscopy was negative. Random biopsy, at the site indicated by barium swallow, proved the presence of carcinoma in 2 cases. Repetition of both examinations is indicated in patients with persistent dysphagia. In 1 case, by barium swallow, partial obstruction of the esophagus was felt to be due to aneurysm, in 2 cases to extrinsic mediastinal tumors, and in 2 cases filling defects were attributed to varices. Ordinarily, fluroroscopic examination is of prime importance, spot films being made of suspicious zones of the esophagus. We have, however, 2 cases in which the

fluoroscopist noticed no abnormality, but he made films that revealed probable carcinoma. The films were made because the patient complained of pain at that particular level.

These cases indicate that roentgenograms of the esophagus should be obtained when there is a history of dysphagia. The patient may be of help in determining the area to be studied, but occasionally his discomfort, as localized by him, will be well removed from the actual site of the disease. In general, he will point to a higher location.

TREATMENT

Too many surgeons dismiss radiation therapy completely in spite of the poor results of surgical therapy. In this hospital, from January 1, 1940 through June 30, 1951 only 7 patients of a total of 170 received any radiation therapy. Ninety-eight of these received no therapy of any kind to the primary lesion.[12] The patient is not a good risk for surgery, the procedure is formidable, and the postoperative period is unpleasant. Block dissection of the ideal cancer type is almost impossible in the mid-thorax due to the presence of the spine, aorta and trachea. In the cervical esophagus there is a strong likelihood of extensive metastases to the cervical lymph nodes.

Watson and Pool[17] mention 2 cases of this type which survived over ten years with combined surgical and radiation therapy, and one that was successfully treated by excision. However, Sweet[15] states, "in the neck and superior mediastinal segment, it is virtually impossible to remove a sufficient number of regional lymph nodes in continuity with the primary growth. The results of surgical extirpation in this group of cases are exceedingly unfavorable and have not been included in the present report." In the lower third of the esophagus the operation advocated by Sweet is indeed formidable but is theoretically more feasible, and his results confirm this. His report of May, 1954[14] gives 17 per cent five year survivals for those patients with carcinoma of the lower section of the esophagus and cardia who survived operation and lived to be discharged from the hospital. (In this article he reports 2 five year survivals in patients with mid-esophageal lesions.) This type of patient would be unlikely to receive any lasting benefit from radiation therapy. There is too often subdiaphragmatic extension of the lesion to the lymph nodes of the cardia or to the liver by the time it is discovered. If the tumor is an adenocarcinoma and the stomach is involved, the tendency in this hospital is to classify it as a primary gastric lesion. Humphreys and Moore[7] have reported on 46 patients who had resections of the esophagus at Presbyterian Hospital, New York City.

There were no five year survivals. The mortality rate was 45.7 per cent, and the average duration of life for the 25 patients who survived the operation was 23 months.

Irradiation difficulties include lymph node invasion and distant extension or metastases. Once the carcinoma has become established in a lymph node its sensitivity is decreased. Thus, a tumor which involves nearby lymph nodes and is relatively localized might be surgically curable and receive little benefit from radiation therapy. On the other hand, a small lesion could involve the trachea or aorta and be nonresectable but curable by irradiation. A series of fields that would cover the primary lesion and all the areas of possible extension or metastases would be too large to permit a probable cancerocidal dose to the volume of tissue being irradiated. In compromise, the fields must be reduced in size or the tumor dose lowered. In spite of this, some encouraging results have been obtained.

Gynning,[5] reporting on 88 patients treated with rotation therapy from 1943 to 1947, had 5 patients free of signs of disease for over five years. Krebs, *et al.*[9] also using rotation therapy, had 1 five year survival of a patient with carcinoma of the middle third of the esophagus. He had treated a

total of 217 patients. Watson and Brown[16] have reported relatively excellent preliminary results using multiport 400 kv. therapy. Of 19 patients 12 were treated and five were apparently well at periods ranging up to 52 months. Of the 7 who died, 4 were autopsied. In these 4 patients there was no evidence of any residual or recurrent carcinoma at the primary site, and in 3 there was no evidence of any tumor. These 3 died of disease that was possibly produced or aggravated by the heavy therapy. One had a mediastinal abscess; the second, reactivation of pulmonary tuberculosis; and the third, coronary disease.

Kohler[8] feels that in general radiation therapy prolongs life on an average of 4 to 6 months, but he had 2 five year cures in 246 cases.

The best results for five years that we have found are those of Gynning.[5] It appears that his technique is also the most meticulous. He has used 170 kv., half-value layer 0.85 mm. Cu, and his target-focus distance is given as 53 cm. The treatments were controlled by constant fluoroscopic observation. The dosage was measured by a sound containing as many as 8 ionization chambers. The sound was centered at the mid-point of the tumor, and direct readings made. The daily tumor dose ranged from 200 to 225 r, and from his series Gynning concluded that the maximum dose should approach, but not exceed, 6,500 r in 35 days, or 6,800 r in 40 days. Gynning did not report his field sizes or his method of determing them. This is obviously important. Various radiologists have used fields of 4×20, 8×10, and 3×15 cm., or any in-between combination. A small tumor may be widely infiltrating the lymphatics. As we cannot adequately irradiate all of the possible extensions, we must decide on the maximum volume and optimum shape of the tissue to be given treatment to a cancerocidal level.

DETERMINATION OF EXTENT OF LESION

The size of the primay lesion should theoretically be the best guide as to the extensiveness of the disease process. But Fleming[3] found metastases in 56 per cent of those patients with lesions less than 5.1 cm. in length, and in 80 per cent of those with lesions larger than 5.1 cm. McCort[10] reviewed 119 cases that were explored and found 80 to have metastases. He saw no relationship between the duration of the symptoms and the occurrence of metastases, or between the size of the primary tumor and the presence of metastases.

In our series there were only 35 cases in which the size of the lesion was accurately recorded at operation or at autopsy shortly after the examination, and in which roentgenograms of the esophagus and chest were available. We wished to know how accurate treatment based on roentgenographic examination would be. We found that the roentgenographic estimate of the length was correct within 2 cm. in 25 of the 35 cases. In 6 of the remaining 10, the involvement was actually less than thought by roentgen examination, and in 4 the length of the lesion was underestimated. The greatest error was in believing a 1 cm. tumor to be 7 cm. in length (Table v).

Twenty-six, or 42 per cent were possibly curable by radiation therapy in this small group. We realize that even carefully done autopsies will not reveal all the hidden minute extensions that, if missed by therapy, would result in failure of the treatment. In spite of this, it seems that radiation therapy should have a better record than it has. It is interesting to note

TABLE V

LENGTH OF TUMOR AND ITS EXTENT

Length of Lesion cm.	Confined to Esophagus	Local Invasion Only	Metastases to Local Lymph Nodes	Distant Metastastes
1.0–3.0	3	1	3	5
3.0–4.9	5	5(4 inop.)	3	10
5.0 and over	5	7(4 inop.)	6	9

that 21 per cent of these patients had tumors confined to the esophagus and were theoretically resectable. If the mortality rate could be reduced to an acceptable level, the salvage rate would be considerably improved. Electrolyte balance is badly upset in these patients. The anemia and general debility of the patient are often difficult to correct preoperatively. Berman[1] has reported optimistically on the use of his polyethylene plastic tube to replace the resected portion of the stomach, but Puestow and Gillesby,[13] Wawro[18] and Hawk and Jeffords[6] have reported very poor results with this mechanism. Nakayama[11] gives an operative mortality of only 11.9 per cent, less than 50 per cent of the best rate reported in this country, but so far we have seen no comment on his work by American surgeons.

There was no correlation between the grade of the tumor and the existence of local or distant metastases. There were 57 cases in which the grade of the tumor and the length of the lesion were given, with the presence or absence of distant metastases. In Table VI the small figures in the corners with the minus signs are those in each category without distant metastases, while the plus signs designate those with distant lesions.

TABLE VI

GRADE AND LENGTH OF TUMOR IN RELATION TO THE PRESENCE OF DISTANT METASTASES

Grade of Lesion	Length, cm.		
	1.0–3.0	3.0–5.0	Over 5.0
I	+1 0	+1 −3	+1 −3
	one	four	four
II	+1 −3	+5 −7	+5 −11
	four	twelve	sixteen
III	+1 −2	+3 −4	+2 +1
	three	seven	three
IV	+1 −1	0 0	+1 0
	two	zero	one

Although Garlock[4] states that metastases to the liver are rare in patients with epidermoid carcinoma of the esophagus, we found such lesions in the liver in 9 of 49 autopsies, or in 18 per cent.

Plus sign indicates number with distant metastases, negative sign relates the number without.

TABLE VII

VISIBLE SOFT TISSUE MASS

	Resectable	Nonresectable	Total
Visible Mass Larger than the Normal Diameter of the Esophagus	2	7	9
No Visible Mass beyond Normal Esophageal Limits	17	22	39

These cases were selected primarily because they were operated upon or because they expired rapidly and autopsies were done soon after the roentgenographic examinations. They do not reflect the resectability of all the cases in this series.

The presence of a visible soft tissue mass about the tumor site is of some help in determining the operability of the lesion (Table VII). We reviewed the films of 48 cases in which the resectability of the carcinoma was later established. In only 2 of the 9 cases with a soft tissue mass projecting beyond the normal limits of the esophagus was resection possible. The absence of a soft tissue mass was only of negative comfort as over half of these were not resectable.

Of the 65 patients on whom radiation therapy was started, 14 died within one month of beginning treatment. Two patients who were accepted for radiation therapy were not included as they died before receiving the first treatment. Thirty of the 65 received only palliative doses or less, due to death during the course of therapy, obvious metastases, or failure of the patient to report for treatment (Table VIII). We have accepted all patients referred to us regardless of condition, feeling there was no alternative treatment in the poor risk patient. We have occasionally been

TABLE VIII

DURATION OF LIFE AFTER DIAGNOSIS ACCORDING TO METHOD OF THERAPY

	No. of Patients	Duration	Comment
No Treatment	40	1.5 mo.	Twenty-eight lived 1 mo. or less, 1 lived 10 mo., 10 lived seven, and 1 five. No 1 year survivals
Gastrostomy or Jejunostomy	59	3.25 mo.	Thirty-seven lived 3 mo. or less, 4 lived over 10 mo. No 1 year survivals
Resection	48	5.5 mo.	Thirty lived less than 1 mo. Two had recurrences treated by irradiation. One patient is still living more than 6 years following resection; 1 after 28 mo. Three 1 year survivals—6.2 per cent
Radiation Therapy	65	5.8 mo.	Twelve still living, 1 for 27 mo., 2 for more than 1 year, 5 from 4–8 mo., and 4 for 3 mo. Five 1 year survivals (2 dead) 9.2 per cent.*
Total	212	4.1 mo.	Two patients treated by resection with irradiation to the recurrences lived more than 1 year.

* This figure was obtained by subtracting the 9 cases still living, but for less than one year, from the grand total of 65 cases treated with irradiation. The difference between the one year survival rate in resected cases and that in those treated with irradiation does not appear to be statistically important.

surprised to see semi-moribund patients gain weight, regain the power to swallow, and feel better generally.

In this institution supervoltage and rotation therapy are not available at present. Factors used are: 200 or 250 kv., half-value layer 1.1 cm. or 1.4 cm. Cu. Distance varies from 50 to 70 cm., the latter being used with large patients. If only palliation is deemed feasible, a tumor dose of 3,000 r is attempted through 4 ports. When cure appears to be possible treatment is given through 6 or 8 ports. Our goal is a tumor dose near 6,000 r in four or five weeks. Our ports are governed by the apparent size of the lesion but vary from 8×10 cm. to 7×14 cm. It has been only two years since we began to mark our patients several times during the course of therapy with the aid of fluoroscopy. The attempt to center these tumors better and to treat them more accurately was started when some patients who were not semi-moribund were referred to us.

SUMMARY

A review has been made of 219 cases of carcinoma of the esophagus. The type of patient predominantly encountered with this disease in this area indicates that diet may be a factor in the etiology, but the data available are not sufficiently detailed to prove this. The use of tobacco and consumption of alcoholic beverages do not appear to be implicated in the development of this disease. While the condition occurs most often after forty years of age, it is occasionally seen in patients in their late twenties and thirties.

A determined attempt should be made to establish the proper diagnosis in any patient with dysphagia, with repetition of the barium study and esophagoscopy in negative cases. It is unlikely that there will be any marked improvement in early diagnosis. Too many patients have extensive disease by the time symptoms develop.

At the present time, it seems logical to treat with radiation therapy those cases

with lesions in the cervical and mediastinal segments. Resection should be attempted in patients with lesions of the lower one quarter of the thoracic segment. The mid-thoracic lesions are subject to more argument. The results with either method of therapy are so poor that it is difficult to justify strict adherence to either form. The grade of the tumor, the duration of symptoms and the apparent length of involvement are of only little value in estimating how effective therapy of either type will be.

In any case, radiation therapy may be worth while for palliation and it should not be withheld, even in patients with extensive disease. A meticulous technique must be used.

107 Ashley Avenue
Charleston, South Carolina

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CARCINOMA OF THE LUNG*

By JAMES J. NICKSON, M.D., EUGENE E. CLIFFTON, M.D., *and* HENRY SELBY, M.D.
NEW YORK, NEW YORK

TREATMENT of cancer of the lung today is, at best, a disappointment. Regardless of the method of treatment, the survival rates are low. Surgical series may indicate as much as 20–25 per cent two-year survival, but only rarely are we told the total number of cases seen. Operability rates range from 20–40 per cent, and resectability rates from one-third to one-half of those explored. Thus, of all cases seen the survival will range from 5–10 per cent two-year survival.

It is emphasized that this paper primarily deals with survival times after treatment. Symptomatic relief can be produced by radiation therapy and is of itself sufficient justification for irradiating patients with cancer of the lung. However, in addition to relief of symptoms, a valid criterion of any form of treatment is its effect on the post treatment span of life. This study inquires into the prospects for survival after irradiation.

In evaluating the contribution of 1 mev. radiation to the management of the primary lesion in this disease the criteria used are (1) survival rates, (2) objective evidence of regression on serial roentgenography, and (3) evidences of symptomatic relief. In order to provide some degree of comparison we have included patients treated with 250 kv. machines as well.

MATERIALS AND METHODS

Cases of carcinoma of the lung treated between 1949–1952 were selected at random for inclusion in this study. These were reviewed first in terms of histology. No cases were included which did not have a positive biopsy, either from the primary lesion or a metastasis, or a positive cytologic examination (Class V). Also, no case is included in which the lung was partially or wholly resected, or in which the primary lesion was not treated in our hospital. All cases so screened were then reviewed by the senior authors. This review included detailed examination of the clinical record and study of all relevant roentgenograms.

In order to facilitate classification of the lesions shown by the patient according to degree of extension, one of us (E.C.) drew up a tentative classification for carcinoma of the lung:

Stage I. *Operable and Resectable Cases*

1. Discrete tumor, roentgenologically not adjacent to the chest wall or merging with hilar shadow.
2. No suggestion of mediastinal lymph adenopathy.
3. Distinct atelectasis of a lobe or smaller segment.

Stage II. *Operable and Probably Resectable Cases*

1. Discrete tumor, roentgenologically adjacent to the chest wall or merging with hilar density or associated with an enlarged hilum.
2. Mediastinal lymph adenopathy by roentgenography or bronchoscopy.
3. A main stem lesion more than 1 cm. from carina.
4. Chest wall invasion adjacent to the tumor.

Stage III. *Operable But Probably Not Resectable Cases*

1. Any case of oat-cell carcinoma; anaplastic.

* From the Departments of Radiation Therapy, Surgery, and X-ray Diagnosis, Memorial Center for Cancer and Allied Diseases, New York, New York. Presented at the Fifty-sixth Annual Meeting of the American Roentgen Ray Society, Chicago, Illinois, September 23–25, 1955.

2. Elevated venous pressure; in arm on affected side, over 150 mm. H_2O.
3. Main stem bronchus involved within 1 cm. of carina.
4. Pleural effusion negative for cancer cells or not studied.
5. Either phrenic or recurrent laryngeal nerve paralysis.

Stage IV. *Non-operable and Non-resectable Cases*

1. Extrathoracic metastases.
2. Metastases to opposite lung.
3. Pleural effusion with proved cancer cells.
4. Both phrenic and recurrent laryngeal nerve paralysis.
5. Combinations of conditions in Class III.

This classification is not put forward as a final classification. However, it is our joint feeling that some attempt to categorize this disease is essential if we are to think in an orderly fashion about the results of treatment. At the present time, there are no accepted methods of staging the extent of this disease as, for example, there is for carcinoma of the cervix. This classification is an attempt to remedy this deficiency. It is hoped that by continued use in our institution and elsewhere that some classification will come to have general acceptance as a means for staging this disease. It is stressed that the findings at operation are not relevant to the staging process.

ROENTGEN TREATMENT

Patients were treated either on the 1 mev. machine or the 250 kv. machine, the latter commonly used with a grid. The factors for the 1 mev. unit are 1,000 kilovolts peak, 3 milliamperes, inherent filtration, half-value layer 3.4 mm. of Pb. Output at 70 cm. target-skin distance is 95 r per minute and at 100 cm. target-skin distance 46.5 r per minute. Most of these patients were treated at 70 cm. target-skin distance. The field sizes ranged from 10 by 12 cm. to 30 by 16 cm. in one instance. Two opposing fields located anteriorly and posteriorly and centering over the affected area were generally used. Treatments with 1 mev. ranged from tissue doses of less than 1,000 r in five days to 6,200 r in fifty days. Commonly the treatments were 200 r midplane dose daily. The average weekly increment was 1,000 r.

Treatments on the 250 kv. machine were usually given with the grid. The grid used was a centimeter square open, a centimeter square closed, in the usual checker board arrangement. The doses are recorded as maximal midplane doses, and range from 1,000 r in eight days to 6,600 r in thirty-nine days. The field sizes were somewhat more uniform for this form of treatment than with the 1 mev. machine because the number of grids available was limited. The smallest field size used was 10 by 8 cm.; the largest used was 15 by 15 cm. The factors for the 250 kv. machine are 30 milliamperes, 1 millimeter Cu filtration added, half-value layer 2.0 millimeters of Cu, target-skin distance 70 cm. The output in air at 70 cm. varies from machine to machine but is approximately 40 r per minute.

Patients were followed by the clinics of the Department of Radiation Therapy and the Thoracic Section of the Department of Surgery. Serial roentgenograms were taken. When hospitalization was necessary, the patients were admitted to beds of either department in a random fashion.

RESULTS

Two hundred cases were considered suitable for inclusion in this study. Several patients who had been treated as carcinoma of the bronchus were rejected, either because of inadequate cytologic or histologic evidence or because the primary lesion, while proved, was not the site of irradiation at our institution. The distribution of cases at various dose levels is given in Table I.

Table II gives the distribution of these cases by age, sex, histology, and staging. It is seen that 22 of the cases were women

TABLE I

DOSE DELIVERED

Dose	1,000 kv.			250 kv. Grid		
	Stage II	III	IV	II	III	IV
1–1,000			3	1	1	2
1,001–2,000	3	1	12	1	2	3
2,001–3,000	7	5	20		8	3
3,001–4,000	8	18	30	1	3	8
4,001–5,000	8	16	16	1	4	3
5,001–6,000	3	2	3		1	3

and 178 were men, a normal sex distribution for this disease. The age distribution for both sexes peaks in the sixth and seventh decades.

The majority of the cases were epidermoid, 107 falling into this category. Thirty-eight were anaplastic, 13 were adenocarcinoma, and 6 were terminal bronchiolar carcinoma. In 36 persons the lesion was of an undetermined histologic type.

There were 33 cases in Stage II, 61 in Stage III, and 106 cases in Stage IV. In Stage I, no cases were irradiated without prior surgery, as all persons with this staging in this institution go directly to the operating room and commonly have resections. It is obvious, therefore, that the bulk of the material to be reported and discussed is derived from experience with patients with far advanced cancer.

The results of treatment are reported by stages. Figure 1 shows the experience for Stage II carcinomas. In this, as in subsequent stages, the cases are divided as follows: (1) those which had exploratory

TABLE II

DISTRIBUTION ACCORDING TO AGE, SEX, HISTOLOGY AND STAGING

Age	Male	Female	Undet.	Epider.	Anapl.	Adeno.	Term.	Stage		
								II	III	IV
31–40	5	1		4	1	1		3		3
41–50	29	3	6	13	11	2		7	9	16
51–60	63	11	14	39	12	6	3	8	18	48
61–70	65	5	12	38	14	3	3	9	27	34
71–80	15	2	4	12		1		5	7	5
81–90	1			5				1		
	178	22	36	107	38	13	6	33	61	106
	200		200					200		

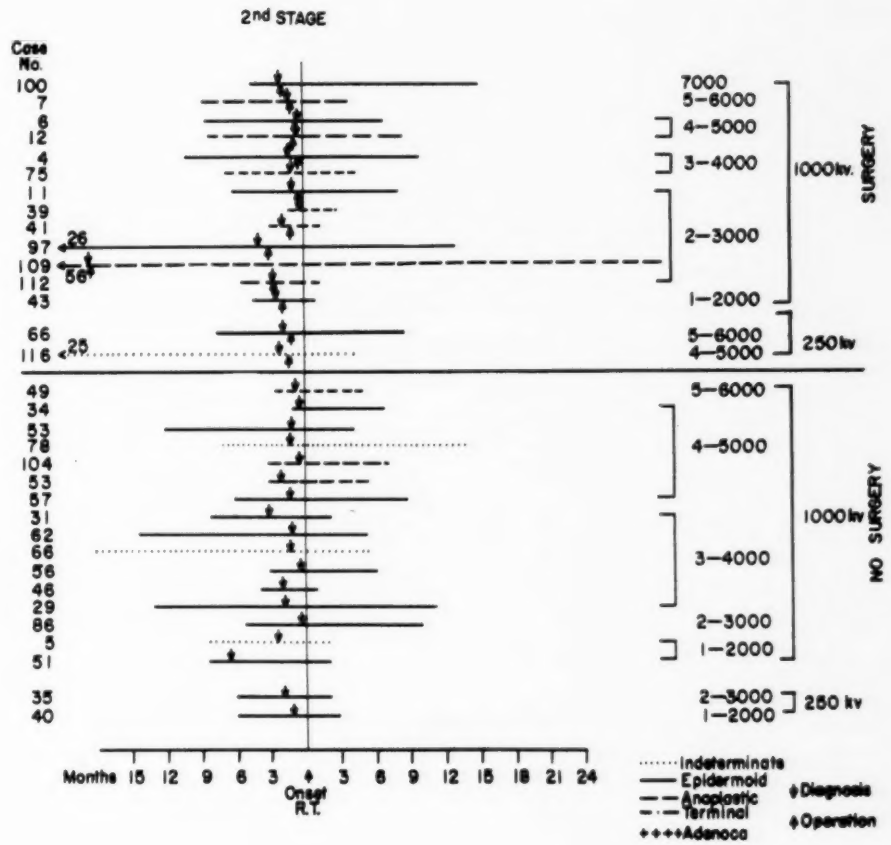


FIG. 1

surgery and those not subjected to surgery; (2) according to the modality of treatment, those treated with 1 mev. being reported in the upper portion of each major grouping; (3) each case is assigned a position in descending order according to the dosage delivered. The dosage represents maximal midplane dosage. The arrow pointing downward indicates the time of diagnosis prior to onset of irradiation. The arrow pointing upward indicates the time of thoracotomy, if any.

The pathology is indicated by the character of the life line for each patient.

Thirty-three cases were classified as Stage II prior to treatment. The average time of survival for this group was 7.4 months. Four patients lived more than 12 months, 1 patient, only, lived more than 18 months. All were treated with the 1 mev. machine with tissue doses ranging from 2,000–6,000 r. Two had epidermoid carcinoma, one had an anaplastic carcinoma, and, in one instance, the histologic type was not determined. It is interesting to note that the patient with the histologic diagnosis of anaplastic carcinoma was the longest survivor in this group, death occurring 31 months after the onset of radiation treatment.

Stage III lesions are reported in Figure 2 in a manner similar to that described for Stage II. In this group there were 61 cases. Three survived 12 or more months. Thirteen of the 61 survived for 3 months or less. Of the former cases, 2 were treated on the 1 mev. machine and 1 was treated on the 250 kv. machine. Histologically, 2 patients had diagnoses of epidermoid carcinoma, and 1 had a diagnosis of anaplastic carcinoma. For all cases the average time of survival was 7.6 months.

In the Stage IV category (Fig. 3, *A*, *B* and *C*) 106 cases are available for analysis. Eighteen

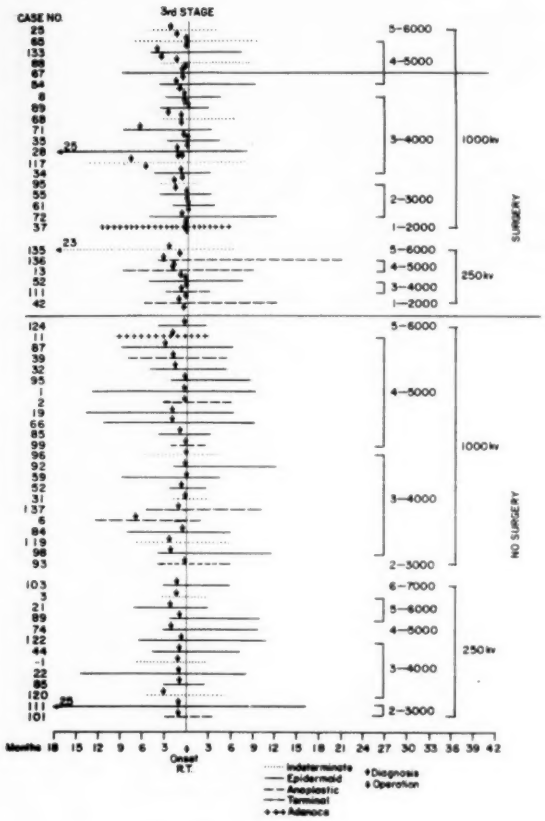


FIG. 2

TABLE III

SURVIVAL IN MONTHS

Stage	Roentgen-Ray Therapy and Chemotherapy		Roentgen-Ray Therapy and Radon Seeds	
Stage II	5.16		7.7	
Stage III	5.56	5.4	8.6	7.9
Stage IV	5.3		7.25	

survived more than 6 months, 10 surviving more than 12 months. Of the 10 cases surviving 12 months or more, 8 were treated with 1 mev., and 2 were treated on the 250 kv. machine. On the other hand, 24 did not survive for a period of three months after the onset of radiation treatment. The average time of survival was 5.4 months.

Some of these patients had radon seeds implanted at the time of the exploratory procedure or received chemotherapeutic agents before, during, or after the irradiation. The 16 cases receiving radon

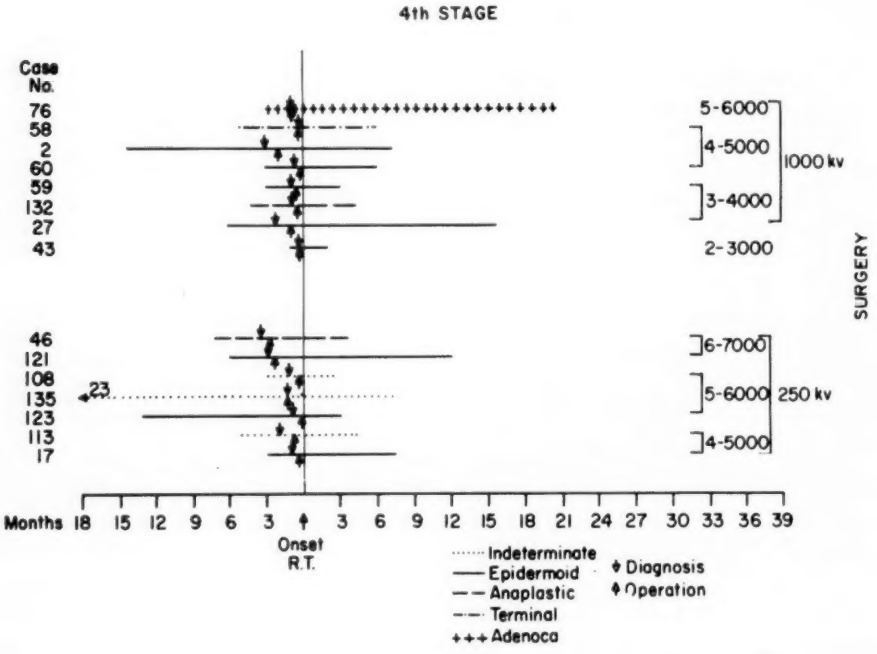


FIG. 3A

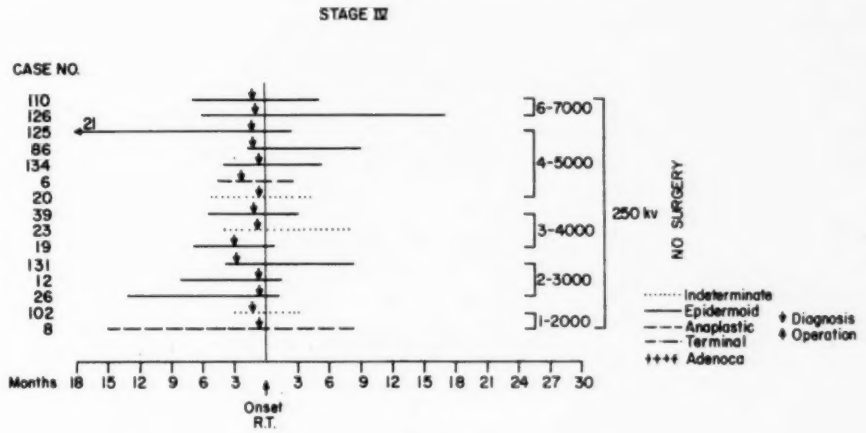


FIG. 3B

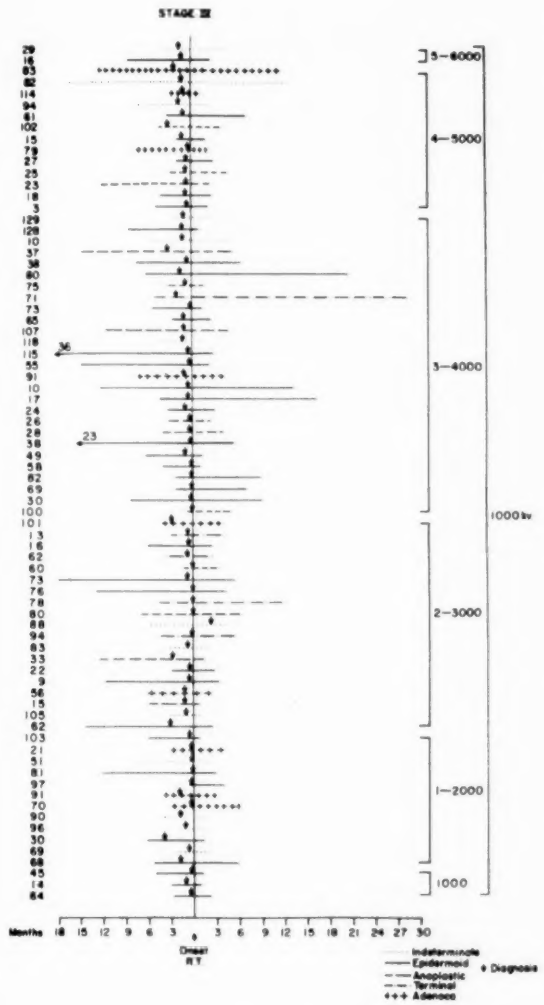


FIG. 3C

seed implantation are outlined in Figure 4. The activities of radon implanted ranged from 10 to 44 millicuries. Only rarely were films available for estimation of tissue dosages on the basis of the volume of the implant. Seven cases in Stage II were so treated. One died between 3 and 4 months after onset of external irradiation. Two survived more than 12 months. In Stage III 5 cases were so treated. Survival time ranged from 4 to 12 months. In Stage IV, 4 cases were also so treated. Survival time ranged from 4 to 12 months. Figure 5 sum-

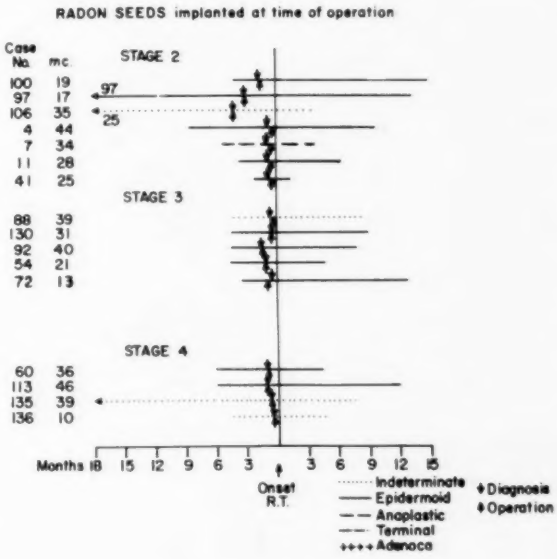


FIG. 4

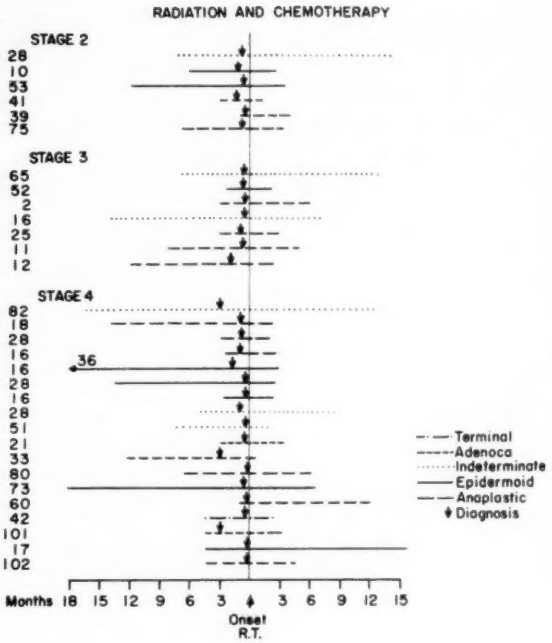


FIG. 5

marizes those cases receiving either nitrogen mustard or TEM, the two chemotherapeutic agents used to supplement radiation in the series. Nitrogen mustard dosage was usually 0.4 milligram per kilogram. Thirty-one cases received supplementary chemotherapeutic treatment. Eighteen of these were classified as having Stage IV carcinoma. Survival times were not long, since, in general, these agents were reserved for those cases strongly suspected or proved to have distant metastases. In Stage IV, for example, 9 of the 18 cases survived 3 months or less.

The relationship of survival by stage is next discussed. For Stage II (Fig. 6), all cases surviving 12 months or longer were treated with the 1 mev. machine. The dose ranged from 2,800 r to 6,200 r. In Stage III (Fig. 7), 5 cases survived 12 months plus. Three were treated with 250 kv., 2 with 1 mev. Dosage ranged from 1,700 r to 4,700 r in this group. In Stage IV (Fig. 8), 13 survived 12 months plus, 3 being treated with 250 kv., 10 with 1 mev. Dosage ranged from 2,700 r to 6,200 r. In this group, the average time of survival for those treated with 250 kv. was 14 months, for those treated with 1 mev., 16 months.

DISCUSSION

Histology. Correlation between survival and histology does not appear to be great in this group of cases. It is interesting to note

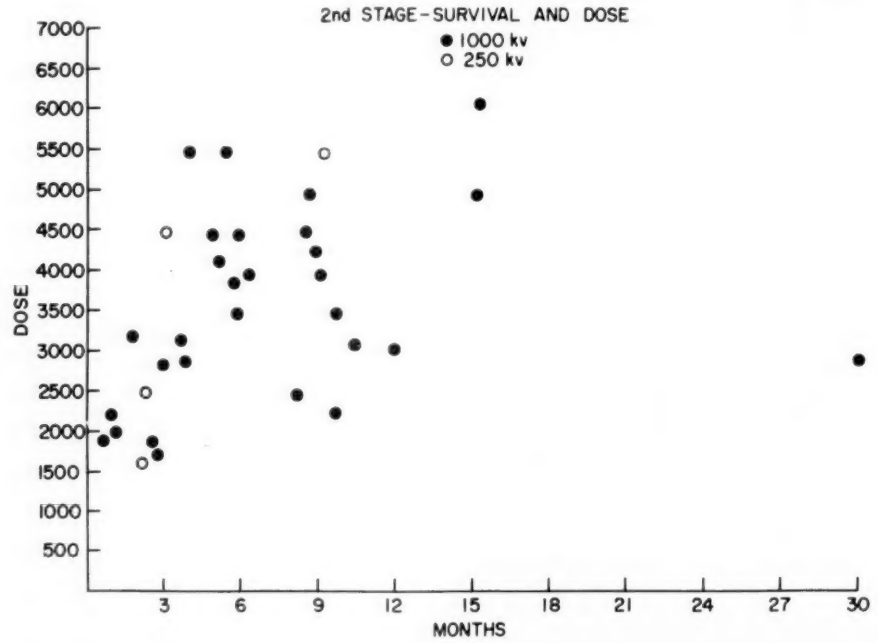


FIG. 6

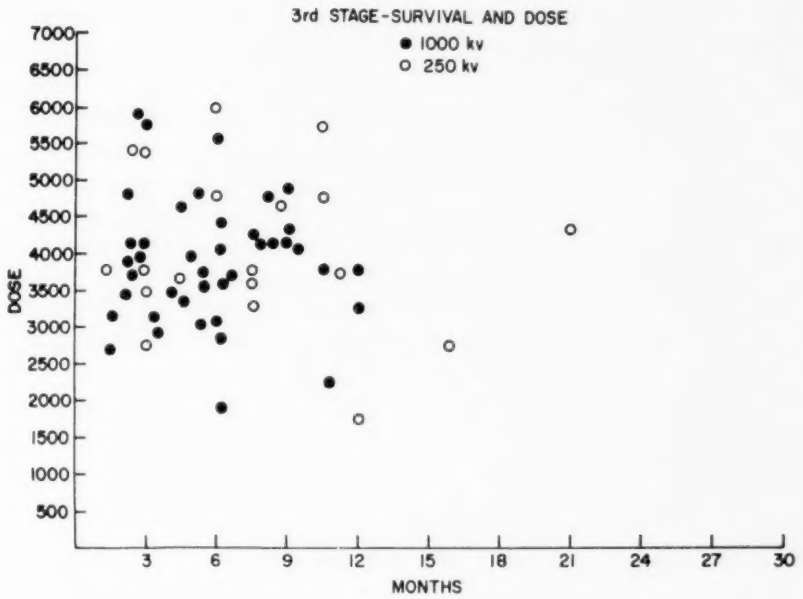


Fig. 7

that in the Stage II group, the longest survivor was a person with anaplastic carcinoma. However, the whole story was so atypical as to make analysis useless in terms of any generalization. This person was a young female. Symptoms strongly suggestive of an intrapulmonary lesion were evident at least 4 years before onset of irradiation. Nineteen months before irradiation, exploratory thoracotomy showed an inoperable cancer of the lung confirmed by histologic study. Thus, survival of 31 months after irradiation is more a result of biologically less active cancer than of the treatment, in our opinion.

Of the remaining cases in this group

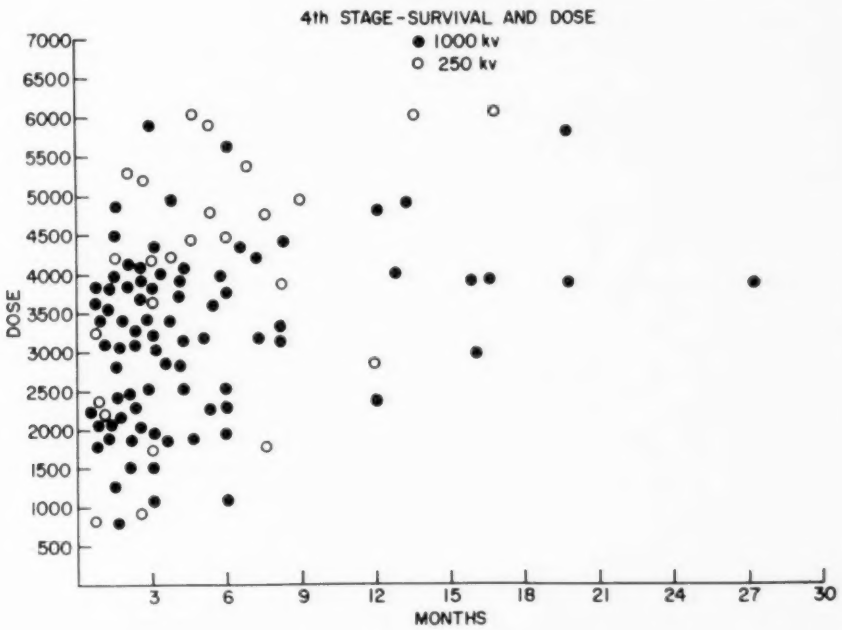


Fig. 8

which survived more than 12 months, 1 cancer was classed as undifferentiated and 2 as epidermoid.

In the cases with Stage III lesions, the longest survivor had an epidermoid carcinoma. Another long survivor, in this instance 21 months, had an anaplastic tumor.

In the Stage IV lesions, it is of some interest that the longest survivor had a terminal bronchiolar carcinoma. Six others had epidermoid carcinomas. Of the 16 patients with anaplastic carcinoma, only 1 lived longer than 12 months.

The Relationship of Surgery to Survival. The average times of survival for each stage comprising the over-all figure with that for surgically explored cases and for cases not explored is shown in Table IV. It is difficult to draw conclusions because it is virtually impossible to assess the selection factor operating within each stage which led to the decision that the given individual was likely to have a resectable lesion. In the Stage II cases 15 were submitted to surgery. Three survived 3 months or less, and 4 survived 12 months or longer. Of the 18 cases not submitted to surgery, the longest survival was 14 months, and 6 survived less than 3 months. While there does appear to be a longer survival in the persons submitted to an exploratory procedure, it does not, in our opinion, follow that this procedure may be considered to be therapeutically beneficial, but rather is an indication of their better general condition.

TABLE IV

SURVIVAL IN MONTHS

Stage II	Surgery	7.7	6.6
	No Surgery	5.9	
Stage III	Surgery	8.2	7.0
	No Surgery	6.2	
Stage IV	Surgery	7.0	5.1
	No Surgery	4.8	

In the Stage III cases, 25 of the 61 patients had exploratory thoracotomies. Four of these survived for 3 months or less. Two survived for a period of 12 or more months. In the cases not submitted to surgery, of which there were 36, only 1 case survived 12 months or longer. Again, the average survival is somewhat more in the explored group but the significance of this fact is questioned. In the Stage IV cases, interestingly enough, 15 cases were subjected to surgery. One of these, having a diagnosis of adenocarcinoma, survived 20 months; 2 other cases survived for 12 months or more. Of the cases not subjected to surgery, there was 1 survival to 28 months, 9 other cases surviving 12 or more months. Ten cases were treated with 1 mev.

In general, as mentioned above, the persons subjected to surgery may be assumed to have disease which, within a given stage, is deemed for whatever reason, more favorable for a radical approach than was the case of a person not subjected to surgery. It is perhaps fair to assume that this judgment may have a positive association with the tendency to a longer survival regardless of the operative procedure performed simply because the extent of the cancer will be somewhat less on the average.

The high proportion of patients in Stage II surviving less than 6 months is of interest. Seventeen of the 33 cases in this group failed to live more than 6 months. This can be contrasted with 44 of 61 cases in Stage III. It might reasonably be expected that the stage of the disease as outlined above should have a correlation with survival. That this did not emerge may be interpreted as throwing some doubt upon the validity of the staging process, or equally, it might be interpreted as indicating that the criteria used are too crude at this time.

Insofar as our data can be interpreted, there appears to be some slight advantage in treatment of the patient with 1 mev. machine as opposed to 250 kv. machines. This conclusion is not statistically valid

and has a further defect in that the data are distorted somewhat by the fact that the assignment to the type of treatment was not done in a randomized fashion. To a degree, randomization may be said to have occurred, inasmuch as a fair proportion of patients were treated with the 250 kv. unit simply because no space could be made available for them on the 1 mev. unit. On the other hand, patients whose disease was far advanced were occasionally treated with the lower kilovoltage because of pessimism on the part of the attending staff member as to the likelihood of marked benefit from treatment. In order to rigidly test the efficacy of 1 mev. as compared with 250 kv., it would be necessary to devise a randomized experiment with assignment of patients to each kilovoltage. Large numbers of patients would have to be treated before any statistically valid conclusion could be reached. In general, it is true that patients treated with the 1 mev. machine suffer less systemic reaction than is the case with the 250 kv. machine. This advantage probably has a real practical application only in the patient with a Stage II or III lesion who is in good general condition, who is working full or part time, and in whom the advantage of obtaining a relatively high tissue dose in a relatively short time is great. It is not likely that the patient with marked symptoms is going to survive long enough from a late Stage III or Stage IV disease to permit the presumed advantages of million volt radiation to become evident.

Of those patients living 12 or more months, of whom there were 19, 16 were treated on the 1 mev. machine and 3 on the 250 kv. machine. The tissue dosage was greater than 3,000 r in all but 5 of all cases treated.

These cases were re-evaluated to see whether there was any pattern in their general state of health prior to the onset of irradiation in the symptomatic response shown or in the objective response shown. No pattern could be discerned which in any way would indicate that pre-selection of cases likely to survive for a long period of time was possible.

Symptomatic response for those cases surviving 12 or more months was fair. For the most part, these patients were able to live fairly comfortably at home. Symptoms were commonly diminished or absent until shortly before their terminal phase. Objective response by roentgen therapy could be evaluated in only about 15 patients. Five showed progression of their lesion, albeit slowly, 6 showed an essentially stationary intrapulmonary situation, and 4 showed regression in their primary.

Review of the interrelationship between objective response and symptomatic response in those cases surviving less than 12 months revealed a poor correlation between objective and symptomatic response.

SUMMARY AND CONCLUSION

1. Two hundred cases of carcinoma of the lung treated at Memorial Center between the years 1949–1952 are reviewed. (These cases are randomly selected from the total experience.)

2. A tentative staging for carcinoma of the lung is presented.

3. There was poor correlation between survival of the patients and the staging of the disease as estimated by the authors on the basis of the evidence prior to surgery or prior to onset of radiation treatment.

4. Survival for these patients differs (if comparable series are analyzed) little, if at all, from that presented in the literature heretofore.

5. Survival does not appear to be influenced appreciably by whether or not supervoltage is used. However, of those cases surviving 12 or more months, of which there were 19, 16 were treated on the 1 mev. machine and 3 on the 250 kv. machine. The significance of this division is discussed.

James J. Nickson, M.D.
Memorial Center for Cancer and Allied Diseases
444 East 68th Street
New York 21, New York

RADIOIRON TRACER STUDIES FOR THE EVALUATION OF RADIATION DAMAGE*

By R. KENNETH LOEFFLER, M.D.
PHILADELPHIA, PENNSYLVANIA

MAJOR interest in the use of radioiron tracer studies to evaluate radiation damage to the erythropoietic system was stimulated by the work of Hennessy and Huff.[9] They were able to demonstrate a decrease in the rate and percentage of incorporation of injected radioiron into red blood cells in individual rats which had received 25 r or more of total body radiation. Statistically, groups of rats having received as little as 5 r could be differentiated from unirradiated rats. The severity of depression is dependent upon the radiation dose, at least up to 250 r (Fig. 1). Belcher, *et al.*[2] have confirmed these results. The present studies were intended to assess the usefulness of one phase of the radioiron turnover test as an adjunct to routine peripheral blood counts in clinical radiation therapy.

Hennessy's data indicate that erythropoietic tissue is as radiosensitive as are the tissues producing white cells and platelets. Because of the life span of the normal erythrocyte, however, complete cessation of production will not appreciably affect the circulating hemoglobin level for one to two weeks. The purpose of the complete radioiron turnover test is to determine the rate of hemoglobin production, permitting appraisal of daily erythropoietic function.[11,25]

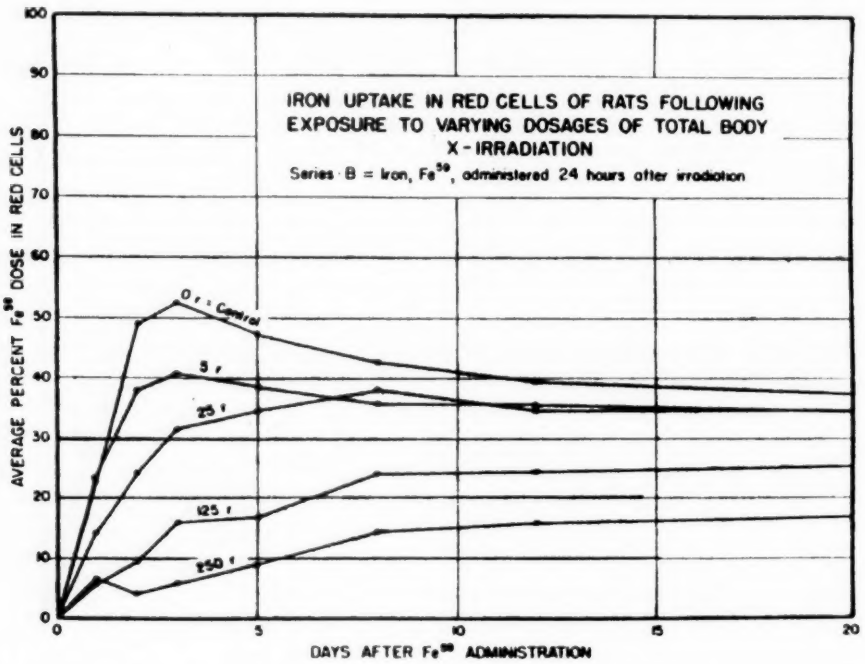
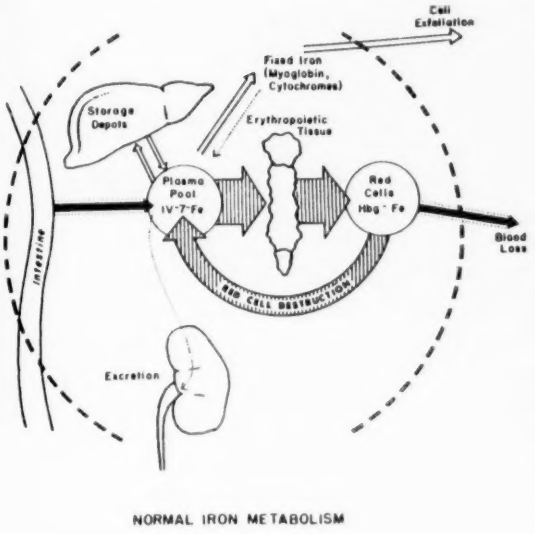


FIG. 1. (Reproduced by permission from *Proc. Soc. Exper. Biol. & Med.*, 1950, *73*, 438.)

These tracer studies should be considered in relation to normal iron metabolism

* From the Department of Radiology, Temple University Medical School and Hospital, Philadelphia, Pennsylvania. Presented at the Thirty-eighth Annual Meeting of the American Radium Society, Houston, Texas, April 9-11, 1956.
This work was aided in part by the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, Contract No. DA-49-007-MD-428.



NORMAL IRON METABOLISM

FIG. 2

(Fig. 2). The iron in the plasma is undergoing continuous turnover in a reasonably steady system. Most of the iron entering the plasma pool is that released from destroyed red blood cells with lesser contributions from storage depots and from the digestive system. Eighty to 90 per cent of the iron leaving the plasma is taken up by the erythropoietic tissues, the rest going to storage depots, to growing tissues for utilization in the cytochrome enzyme systems, and several milligrams per day being excreted in feces, urine, and sweat. The normal plasma iron concentration is about 0.1 mg. per 100 ml. of plasma. The normal red blood cell life span being about 120 days, each 100 ml. of plasma has to transport about 1 mg. of iron per day to the bone marrow for hemoglobin production. Thus, it is evident that the plasma iron must be replaced about 10 times per day. The iron concentration alone does not permit estimation of the turnover rate. By injecting a radioactive tracer into the vascular system and determining the activity of successive blood or plasma samples, the clearance rate can be measured.[24] This radioactive tracer follows the same metabolic pathways as does the native plasma iron present at the time of injection. A reasonably constant portion is cleared by the erythropoietic tissues, the liver and other storage depots, and miscellaneous tissues with each circulation. While nonradioactive iron enters the circulation to replace that being removed, the radioactive component is continually being depleted. Since a constant fraction is cleared with each circulation, the decrease in activity is exponential; the rate of decrease may be defined by the time required to reach half of the initial activity—the half-time. Plasma iron clearance is calculated from the equation:

Micrograms iron cleared per hour per 100 ml. plasma =

$$\frac{0.693 \times \text{plasma iron concentration in micrograms \%}}{\text{Half-time of disappearance in hours}}.$$

The hourly clearance of iron from the entire plasma pool is calculated from the clearance per 100 ml. and the plasma volume. The plasma volume is obtained from the initial dilution factor of the injected tracer, as part of the clearance rate test. The daily clearance is approximately 24 times the hourly clearance, but is subject to uncertainty due to diurnal changes in iron concentration, plasma volume, and half-time.[3,20] Since a variable portion of the iron leaving the plasma is incorporated into red cells, this percentage must be experimentally determined in order to calculate daily hemoglobin production. Whole blood samples are analyzed for radioactivity until a plateau is reached, usually at 5–7 days, and total red cell radioactivity expressed as percentage of injected activity. Hemoglobin production is calculated from the equation:

Hemoglobin produced per day (grams) =

$$\frac{16.6 \times \text{plasma vol. (ml.)} \times \text{plasma iron conc. (mg./ml.)} \times \text{percentage utilization}}{\text{Disappearance half-time (hours)} \times 3.34 \text{ (mg./gm. hgb.)}}.$$

Because of the interdependence of the four variable factors, some authors report only the computed daily hemoglobin production. While the level of hematopoietic activity is not determinable from any of the variables independently, such condensation fails to utilize the available data to the maximum extent.[6–8,13,14,18,19,27,29] Over 700 iron turnover tests have been performed by this department in the past three years as a laboratory routine for the differential diagnosis of hematopoietic disorders.[25] The observed values for some conditions are presented in Table 1. In general, half-times of less than normal are observed when anemia is present despite adequate erythrogenic activity, and prolonged half-times when anemia is on a hypoplastic basis.

The usefulness of radioiron tracer studies for evaluation of radiation damage results from the quantitative assessment of induced hypoplasia. Decreased erythropoietic activity is usually characterized by long half-time, high plasma iron concentration, and poor utilization of the cleared iron. The animal studies of Hennessy and Huff[9] correlate the last variable with dose of radiation.

Huff and his co-workers have also used the change in plasma iron clearance half-time as an index of marrow depression by radiophosphorus in the treatment of polycythemia vera.[11] The clearance rate would be a more satisfactory variable than the percentage uptake to use as a therapeutic control, if equal usefulness could be established. The clearance rate can be determined in 1–3 hours. Since the plasma is cleared of significant activity within 24 hours, tests can be repeated daily. The percentage uptake cannot be dependably determined until a plateau in the red cell radioactivity has been reached, which may take from 5 to 7 days. If a second tracer is given before a plateau has been obtained from the first, it is impossible to determine the percentage incorporation of each. After several radioiron studies, the red blood cell radioactivity becomes sufficiently high that additional activity is difficult to determine accurately.

Table I

Hematologic Condition	FE_{P-C}	T/2	Uptake
	UG %	Hours	%
Normal	60–110	1–2	Up to 90% in 1 week, then plateau
Anemia			
Iron deficiency	0–50	0.3–0.5	Approaching 100% in 3–4 days, then plateau
Chronic blood loss	0–50	0.3–0.5	Approaching 100% in 3–4 days, then steady fall-off
Hemolytic	40–70 (Occ. high)	0.3–0.5	Approaching 100% in 3–4 days, then plateau
Chronic infections, Malignant tumors, Leukemia, Liver diseases	40–70	0.3–1	Approaching 100% in 3–4 days, then plateau
Aplastic	150–300	2–6	Very low and slowly rising
Addisonian			
Untreated	150–200	0.3–0.6	Slow rise over many weeks, no plateau
Remission			
early	40–70	0.3–0.4	Approaching normal
late	60–110	1–2	
Mediterranean	150–200	0.3–0.6	Slow rise over many weeks, no plateau
Polycythemia			
Primary, untreated	50–100 (Occ. high)	0.3–0.5	Approaching 100%
Remission	60–110	1–2	Normal
Repeated phlebotomy	40–70	0.3–0.5	Approaching 100%
Secondary	50–100 (Occ. high)	0.3–0.5	Approaching 100%
Hemochromatosis	200–250	1–2	Low uptake

This difficulty can be overcome by administering successively larger tracer doses, but the acceptable human tracer burden is soon reached. A serious disadvantage of the half-time alone is that the site of clearance is not indicated. As erythropoietic activity is depressed, an increasing portion of the plasma iron is cleared by the liver. The present studies were conducted to determine whether this uncertainty negates the value of the test as an adjunct to routine blood cell counts for the evaluation of systemic tolerance in the practice of radiation therapy.

The study had three phases:

1. Correlation of change in half-time with change in peripheral blood picture and with symptomatology in patients receiving therapeutic levels of total body radiation.

2. Similar comparison in patients receiving radiation through limited portals.

3. Investigation in rabbits of an extended procedure using turnover studies to detect residual hematopoietic damage at longer time periods following total body radiation, when the peripheral blood levels have returned to normal and the individual has apparently returned to pre-irradiation status.

INVESTIGATIONS

1. Sixteen persons, including staff personnel with apparently normal hematopoietic systems and patients with a variety of disorders not directly related to the hematopoietic system, had two or more determinations of their plasma iron clearance rates at varying intervals. The variation between any two half-times on the same individual was less than 30 per cent in eighty-two of the eighty-eight possible comparisons. When summarizing subsequent data, change of less than 30 per cent was not considered significant.

Thirty patients with generalized neoplastic disease received total body radiation in doses ranging from 100 to 200 r in single exposures, and from 250 to 550 r total when fractionated.[5,23] Dose is described as skin dose to the mid-surface of the patient, the

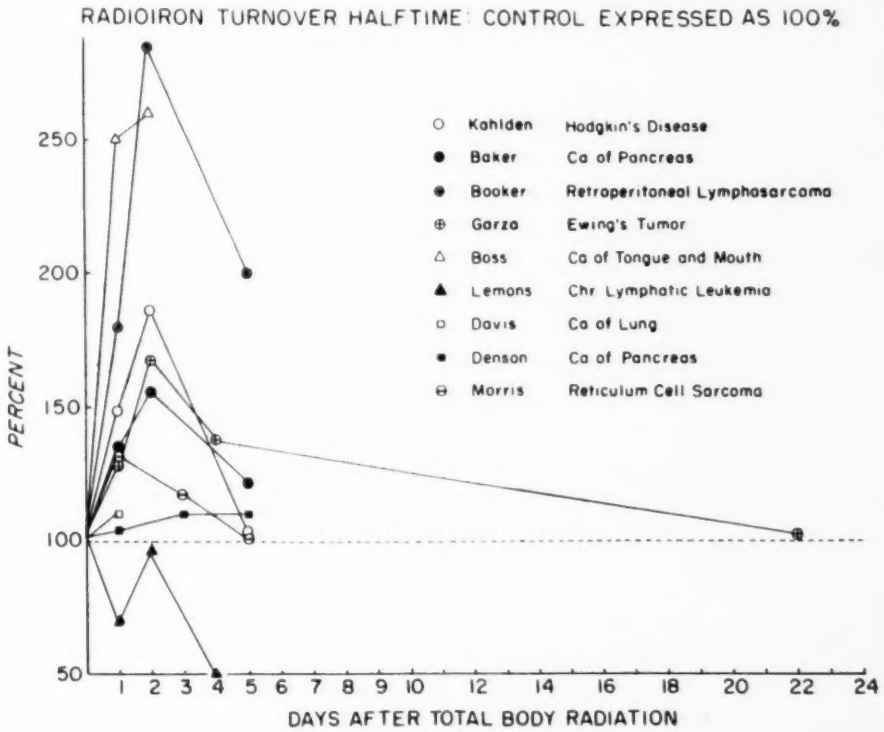


Fig. 3

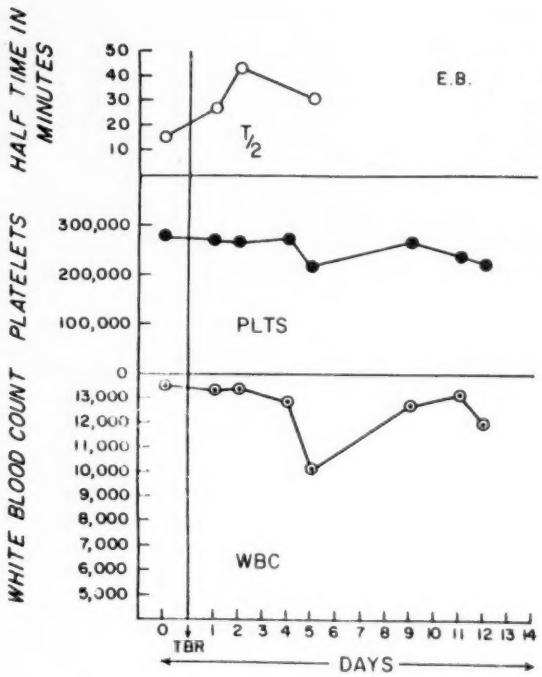


FIG. 4

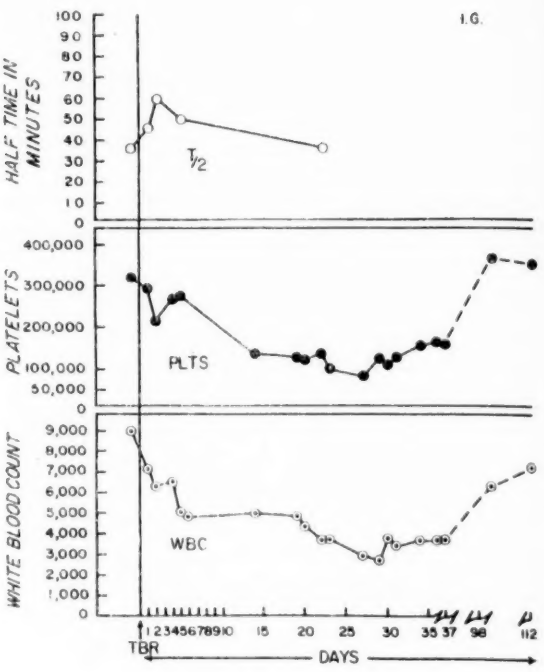


FIG. 5

radiation factors being 250 kv. peak, half-value layer of 1.2–2.3 mm. Cu, target skin distance of 360–400 cm. Changes in half-time after irradiation for 10 of the patients who received 200 r to the anterior body surface are shown graphically in Figure 3. Daily variation in peripheral blood counts and in radioiron half-time of 3 of these patients is shown individually in Figures 4–6. The last of these shows the changes following two doses of 200 r each, separated by five months. Data on the 30 patients are summarized in Table II, grouping patients with approximately equal radiation exposure. The plasma clearance rate is altered about as frequently as is the platelet and white blood cell count. Change in laboratory data is more frequent than is symptomatology in this dose range. Change in clearance rate occurs more promptly than does change in blood cell count and shows more rapid return to normal. Some patients had alteration in only one or two of the functions studied.

2. Thirty-eight patients received fractionated radiation therapy through limited portals. The percentage change in half-time for each is shown in Figure 7, plotted as a function of energy absorbed. The plasma iron half-time was determined within three days prior to the beginning of therapy, and again on the last or next to the last treatment day. Integral dose is calculated as

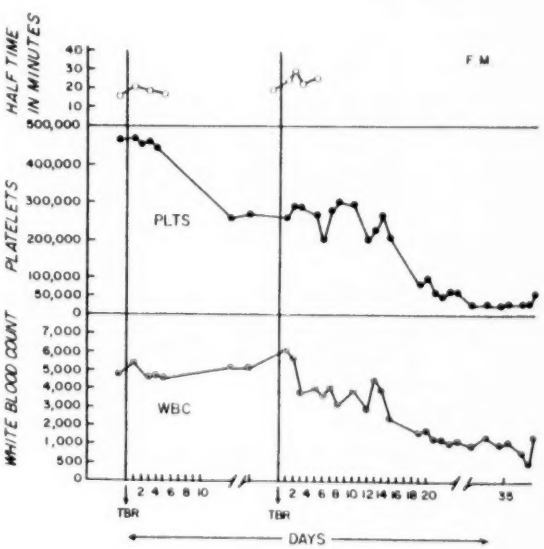


FIG. 6

Table II

Dose	Symptoms	WBC	Platelets	FE
100 r	0/1	1/1	1/1	1/1
125 r	0/1	1/1		1/1
150 r	0/1	1/1	0/1	1/1
200 r including 1st rx	7/23	16/23	16/19	11/17
200 r+100 r (5 wk.)	0/1	0/1	0/1	0/1
200 r+200 r (5 mo.)	1/1	1/1	1/1	1/1
200 r+200 r (3 wk.)	1/1	1/1	1/1	
50 r×5	0/3	3/3	3/3	1/2
55 r×10	1/1	1/1	1/1	1/1

x/y indicates number of patients showing a change out of the number studied for the item in question.

described elsewhere.[26] No attempt has been made to compensate for the dependence of effect upon both time and dose, since there are no useful factors available which would permit meaningful adjustment of stated values to a common baseline. Since most patients were treated over a three to five week period, such adjustment would likely be of little importance. No correlation is evident between integral dose and slowing of the plasma clearance rate. Grouping the patients by region treated or by tumor dose does not improve the correlation. Further comparison of the change in half-time with change in white blood cell count, platelet count, or with symptomatology during treatment, clinical recovery following treatment, and longevity following therapy likewise fail to reveal any useful trend.

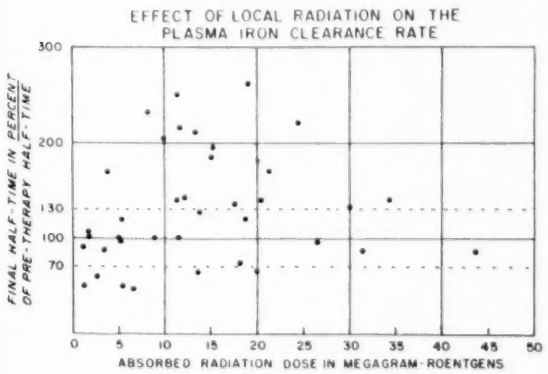


Fig. 7

Laboratory data are given in Table III on 2 patients with seminoma who received a mid-point tissue dose of 1,500 r in three weeks to the lymphatic drainage areas of the pelvis and abdomen, through opposing anterior and posterior fields totaling 500 square centimeters to each side. Plasma clearance rates were determined at weekly intervals. The half-time of each slowed at first then recovered as treatment continued. These changes may reflect an initial depression of marrow function within the treated volume, followed by compensatory hyperfunction of unirradiated erythropoietic tissues. The white blood cell count continued to decline during treatment, consistent with the decrease in residual tolerance as absorbed dose increases. Possibly an occasional patient would show a dramatic slowing of the plasma iron clearance rate without subsequent recovery, indicating that erythropoiesis will limit the tolerable dose. The data given suggest that

Table III

Patient J.N.
Tumor Dose—1,500 r/3 wk.
Integral Dose—26.6 megag. r/3 wk.

	Pre-therapy	End 1st Week	End 2nd Week	End 3rd Week
WBC	14,500	9,300	5,500	5,250
Platelets	236,000	224,000	194,000	166,000
HGB	12.8	13.3	12.0	11.9
T/2	82′	75′	127′	76′
FE_c	85	115	127	93

Patient W.M.
Tumor Dose—1,500 r/3 wk.
Integral Dose—31.4 megag. r/3 wk.

	Pre-therapy	End 1st Week	End 2nd Week	End 3rd Week
WBC	12,700	6,900	7,400	4,950
Platelets	264,000	288,000	184,000	256,000
HGB	13.8	14.2	13.5	12.6
T/2	102′	142′	145′	87′
FE_c	121	149	164	103

this will occur infrequently, if at all, with local irradiation.

3. A preliminary experiment was conducted to develop a method for measuring residual hematopoietic damage. Most organs of the body are able to increase their functional level when the need arises, although this reserve capacity is not usually evident or measured. Of 2 persons, each with a normal hemoglobin concentration, it may be that one could greatly increase hemoglobin production in response to a demand created by bleeding, hemolysis, or hypoxia; while the other is just barely able to maintain a normal level, and could not increase erythropoiesis even should the need arise. Prior to the stimulus for increased production, routine hematologic examination would not reveal any difference between the 2 persons. A decrease in reserve capacity could partially explain the greater response to a second equal dose of radiation, which is usually observed even when no residual damage from the first dose is apparent. One patient illustrated this increased response to total body radiation (Fig. 6). This patient had generalized lymphosarcoma, but was otherwise in good health. He was given 200 r skin dose to his anterior body surface, radiation factors being 250 kv. peak, half-value layer of 1.2 mm. Cu, target skin distance of 400 cm. He developed no symptoms, and no significant change in white blood cell count or plasma clearance rate. The platelet count remained within normal limits despite a late drop. The generalized lymphadenopathy disappeared, and the patient had no gross evidence of disease for five months, when the lyphadenopathy returned. Findings on physical examination and peripheral blood study were similar to those of five months previously. Yet a second dose of 200 r caused nausea and vomiting for three days with considerable change in white blood cell and platelet counts and plasma iron clearance rate.

If loss of reserve capacity of various body systems does explain some of the residual damage from radiation, it should be possible to demonstrate the defect by presenting a stimulus for increased activity of a system and observing an inadequate response. Rabbits were chosen for study because they are large enough to permit repeated venipunctures and are available in reasonably homogeneous strains. Change in plasma iron clearance rate was used as an index of alteration in function. Hypoxia was adopted as a stimulus,[12,21,22] the rabbits being maintained in a decompression chamber at two thirds atmosphere. The standard radiation dose was 500 r surface dose, 250 kv. peak, half-value layer of 1.2 mm. Cu, target skin distance of 100 cm., delivered from above to the back of each rabbit in a 40×40 cm. box filled with rice bolus. Clearance rate determinations were limited to two per rabbit, since significant blood loss would act as a stimulus similar to hypoxia, with additional changes possibly resulting from removal of other blood elements. The plasma iron clearance rate of each animal was determined initially, and again at varying times after being subjected to one of the three experimental conditions.

The first group was given 500 r total body radiation. Each rabbit had a second half-time determination within two weeks following irradiation. In Figure 8 is shown the change in half-time with time after irradiation. Each point on the curve represents 10 rabbits. The shaded area represents fewer animals, and demonstrates the variability in time required for the half-

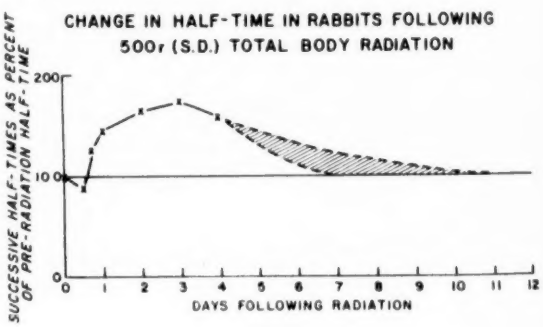

CHANGE IN HALF-TIME IN RABBITS FOLLOWING
500r (S.D.) TOTAL BODY RADIATION
SUCCESSIVE HALF-TIMES AS PERCENT OF PRE-RADIATION HALF-TIME
200
100
0
0 1 2 3 4 5 6 7 8 9 10 11 12
DAYS FOLLOWING RADIATION

FIG. 8

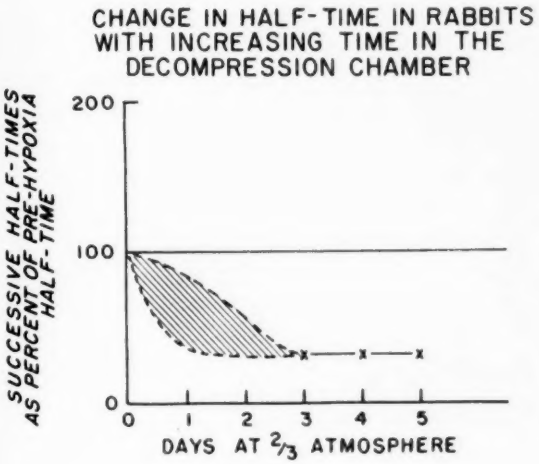

CHANGE IN HALF-TIME IN RABBITS WITH INCREASING TIME IN THE DECOMPRESSION CHAMBER
SUCCESSIVE HALF-TIMES AS PERCENT OF PRE-HYPOXIA HALF-TIME
200
100
0
0 1 2 3 4 5
DAYS AT 2/3 ATMOSPHERE

Fig. 9

time of individual rabbits to return to normal.

The second group was placed in the decompression chamber at two thirds atmosphere for from one to five days. As shown in Figure 9, the iron clearance half-times became shorter. The half-time changes were quite variable until the third day, after which almost all rabbits had half-times of thirty to forty minutes.

The third group was irradiated to 500 r, and after varying periods of time each rabbit was placed in the decompression chamber for three days. The second clearance rate determination was performed immediately after removal from the chamber. Eighteen rabbits were used in the preliminary phase of this experiment. As shown in Figure 10, the results were not sufficiently consistent to warrant repetition with a larger group of rabbits under the same experimental conditions. Rabbits which were irradiated and immediately placed in the decompression chamber for three days, had slow half-times similar to those of rabbits receiving radiation alone. This was expected, as it was considered unlikely that excess stimulus could overcome the damage caused by radiation. Several of the rabbits maintained at atmosphere pressure for a week or longer after irradiation, then subjected to three days of hypoxia prior to the second clearance rate determination, demonstrated the inadequate response to hypoxia which was anticipated. However, some rabbits, having had only five to nine days to recover from 500 r, already showed a normal response to the erythropoietic stimulus.

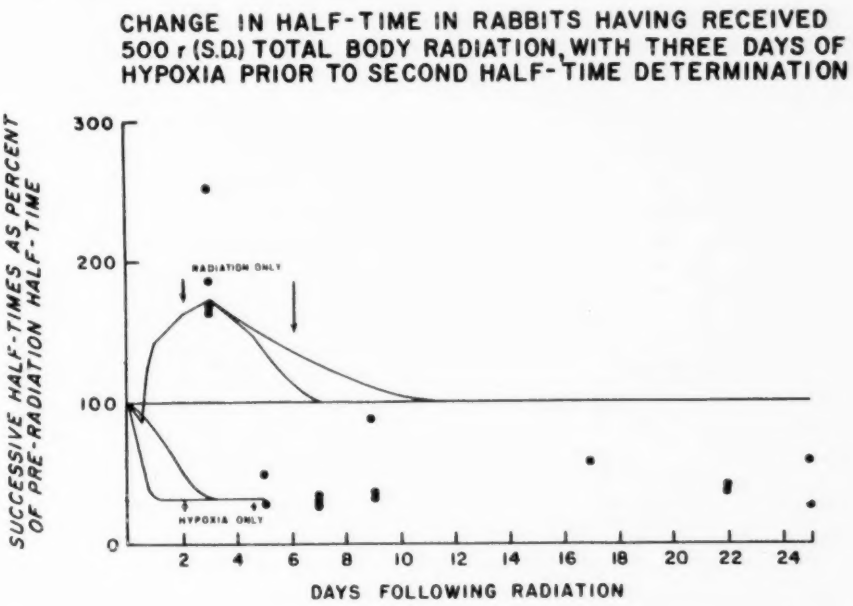

CHANGE IN HALF-TIME IN RABBITS HAVING RECEIVED 500 r (S.D.) TOTAL BODY RADIATION, WITH THREE DAYS OF HYPOXIA PRIOR TO SECOND HALF-TIME DETERMINATION
SUCCESSIVE HALF-TIMES AS PERCENT OF PRE-RADIATION HALF-TIME
300
200
100
0
RADIATION ONLY
HYPOXIA ONLY
2 4 6 8 10 12 14 16 18 20 22 24
DAYS FOLLOWING RADIATION

Fig. 10

These data are not sufficient to either prove or disprove the concept of decreased functional reserve as a radiation residuum. They are certainly too inconsistent to suggest a potential clinical test.

DISCUSSION

Radioiron tracer studies are of clinical value for the diagnosis of anemias, the etiology of which is not completely apparent from less esoteric examination, and for the diagnosis and control of therapy of polycythemia vera. As a research tool, radioiron has been used as a tracer for the elucidation of various pathways and mechanisms of iron metabolism, for the quantitative evaluation of the effects of whole body irradiation in animal species, for the study of the mode of action of radiation upon the erythropoietic system, and for the appraisal of agents which may stimulate or depress erythropoietic function.[1,15–17,28]

In the initial studies on rats by Hennessy and Huff,[9] iron was injected at varying times following irradiation and the rate of red blood cell incorporation determined. The best correlation between dose of radiation and reduction of incorporation was noted when the iron was injected 24 hours after irradiation. Greater time delay resulted in varying degrees of recovery, the rate of recovery also being dependent upon the dose administered. With doses of less than 200 r, the initial depression for several days was followed by a return past normal to an increased utilization for several days.[10] This overcompensation may be due to the stimulus of the slightly decreased hemoglobin resulting from the period of depressed hematopoietic activity.

The relationship between dose of radiation and depression of iron utilization is more nearly exponential than linear, with successively larger doses being required to cause additional equal depression. It has been postulated that this relationship indicates direct damage to the red blood cell precursors, inhibiting their ability to divide and produce new red blood cells. An alternative explanation would be that radiation blocks one or more of the reactions involved in hemoglobin formation by direct inhibition of some enzymes. Evidence for the direct effect of radiation on red blood cell precursors is provided by studies of Lajtha and Suit.[17] These workers investigated the utilization of radioiron by bone marrow cultures using radioautographic techniques, and noted that iron was incorporated into the developing cells primarily during the late pronormoblast and basophilic normoblast stages. When the marrow cultures were irradiated and iron incorporation studied at successive intervals thereafter, it was noted that the accumulation of radioiron by cells of a given developmental stage was not impaired. Immature cells continued to progress toward more mature forms, but no new cells were produced. A gradually shifting cell population resulted. Within several days after irradiation, cells at the iron-accepting level of development were almost entirely absent, and iron incorporation by the culture practically ceased. These studies provide direct evidence on the mechanism of radiation damage, which explains our *in vivo* observation that maximal depression of the plasma iron clearance rate occurs about three days after total body irradiation in humans and in rabbits. The failure of the plasma iron clearance rate to change in proportion to the dose of partial body irradiation is also consistent with a direct effect of radiation upon marrow cells. Hennessy[10] studied the utilization of iron by rats having received varying doses to the abdomen from sharply defined beams of deuterons, positioned to avoid all bone marrow. Even though the rats showed other radiation effects, none, even those having received a lethal dose, showed change in iron utilization.

Radioiron tracer studies have been shown to be of value for the evaluation of erythropoietic depression following the administration of systemic agents and deserve more widespread use. Lawrence and co-workers[21] have already established the usefulness of the test to control the treat-

ment of polycythemia vera by radiophosphorus. That most chemotherapeutic agents used for the treatment of patients with cancer are hematopoietic depressants is accepted; that such depression is reflected in the iron turnover test has been shown. The intent of treatment is usually to cause the greatest possible controlled destruction from which the patient can satisfactorily recover. Any additional examination or test which can help establish this limit should be utilized whenever possible.

The problem of measuring residual radiation damage may become one of major importance. At the present time only a relatively few persons are exposed to radiation, usually in a manner which is controllable and can be held to an insignificant level. With the likely increase in the number and types of nuclear reactors, it is possible that a much larger portion of the population will join the chronically exposed group. It may be that the further economic development of the country will some day necessitate a relaxation of the present permissible tolerance levels. Should this necessity arise, possible radiation damage may become accepted as an industrial hazard with a known calculated risk, similar to silicosis in miners or the possibility of falling among construction workers. A method for measuring damage before it becomes grossly evident and irreversible would then be of value. The leukopenia and anemia which are occasionally observed in persons having received prolonged chronic exposure are apparently almost irreversible. This is consistent with the concept of a gradual depletion of reserve functional capacity. Even though the experiment reported above failed to confirm this concept, the conditions chosen may not have been adequate.

Should the basic concept prove useful, other methods of demonstrating the residual radiation defect will have to be found. To spend several days in a decompression chamber is feasible as a research procedure, but not practicable as a routine for thousands or millions of persons. Possible alternatives are apparent. There is some evidence of a circulating hormone which stimulates erythropoiesis. Should this hormone be isolated, it could serve in lieu of hypoxia as a maximal stimulus. Other radiosensitive tissues or functions other than erythropoiesis should be studied. A variety of insults to the body cause a leukocytosis. Perhaps a reasonable quantitative response to an injection of dead bacteria could be established as a test system. The production of hydrochloric acid by the gastric mucosa is depressed by acute radiation exposure. If this function is also depressed by chronic low-level exposure, the alcohol-histamine test is already available as the stimulus for maximal production. It is disappointing that this study was unsuccessful, but the problem of residual radiation damage is considered of sufficient importance to warrant further efforts.

SUMMARY

The plasma iron clearance rate was determined during and following treatment in cancer patients receiving total body and limited field irradiation. Slowing of the clearance rate as an index of erythropoietic depression, was compared with radiation dosage, symptomatology, and other laboratory evidence of systemic depression. These data suggest the usefulness of radioiron tracer studies on a routine basis for early indication of impending intolerance to generalized therapy for cancer. No useful correlation was observed with limited field irradiation.

Extension of radioiron tracer studies to provide a test for residual radiation damage is described and discussed, even though a preliminary experiment failed to indicate a useful technique.

3401 North Broad Street
Philadelphia 40, Pennsylvania

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CORRELATION OF IODINE 131 CLEARANCE RATE FACTORS WITH CARDIAC FUNCTIONAL STATUS, PROTEIN-BOUND-IODINE PLASMA VALUES, AND BLOOD NONPROTEIN NITROGEN

By I. MESCHAN, M.D.,[1] T. H. ODDIE, D.Sc., F. INST. P.,[2] JAMES T. WORTHAM, M.D.,[3] J. E. DOHERTY, M.D.,[4] *and* ELVIS LITTLE, M.D.[5]

DETAILED mathematical discussions, practical test methods and some results have been published, relating to k_1, the thyroidal iodide clearance rate factor, and k_2, the renal iodide clearance rate factor.[2,3,4] The parameter k_1 is the fraction of the total iodide space cleared of iodide per minute by the thyroid gland; and k_2 the fraction of the total iodide space cleared by the kidneys per minute.

When all data are analyzed, the hypothyroid-euthyroid boundary for k_1 has been interpreted as approximately 0.23×10^{-3} minute^{-1}; and the hyperthyroid-euthyroid boundary as $k_1=3.85\times10^{-3}$ minute^{-1}.

The renal rate factor, k_2 has little significance as far as thyroid function is concerned, but it does affect the observed 24-hour percentage uptake. Thus, a value of $k_1=3.85\times10^{-3}$ minute^{-1}, and the average renal rate $k_2=2.2\times10^{-3}$ minute^{-1} is equivalent to a 62 per cent 24-hour uptake observed with our collimator, or a plasma clearance rate of 63 ml./minute.

The non-cardiac range for k_2 has been established at:

$$0.09 \text{ to } 3.90\times10^{-3} \text{ minute}^{-1}.$$

Moreover, it is our experience that the borderline zone between euthyroid and hypothyroid is not sharply defined and extends between:

$$k_1=0.18. \text{ to } 0.23\times10^{-3} \text{ minute}^{-1}.$$

Although some results relating iodine uptake to protein-bound-iodine plasma values (P.B.I.) and cardiac status have been published,[1,5] the clearance rate studies such as we have performed have afforded us an additional opportunity for attempted correlation and these are described below.

METHOD OF STUDY

In the course of random determinations of k_1 and k_2, 68 patients with cardiac disease were thus studied, and of these, 49 also had P.B.I. and N.P.N. (nonprotein nitrogen) determinations, as well as rather complete cardiac status evaluations. (New York Heart Association Standards.)

The various etiologic types of heart disease included and their functional classification are given in Table 1.

It is noted that arteriosclerotic heart disease (23 patients), hypertensive heart disease (18 patients), and rheumatic heart disease (15 patients) were in greatest number, with scattered representations in other types. Also, there was good sampling in functional Classifications II, III, and IV with very few (4 patients) in I.

The following relationships have been studied: (1) Functional cardiac status and k_1; (2) functional cardiac status and k_2; (3) P.B.I. and k_1; (4) P.B.I. and k_2; (5) N.P.N. and k_1; (6) N.P.N. and k_2.

THE RELATIONSHIP OF CARDIAC FUNCTIONAL CLASSIFICATION WITH *k* VALUES

Thyroidal rate k_1. If the normal range for k_1 is indicated as: 0.18 to 3.8×10^{-3} minute^{-1}, the following observations are warranted:

1. Twenty-five per cent (17 patients) of

[1] Professor and Head, Department of Radiology, Bowman Gray School of Medicine, Winston-Salem, North Carolina.
[2] Associate Professor of Physics, Department of Radiology, Bowman Gray School of Medicine, Winston-Salem, North Carolina.
[3] Associate Professor, Department of Medicine, University of Arkansas School of Medicine, Little Rock, Arkansas.
[4] Assistant Professor, Department of Medicine, University of Arkansas School of Medicine, Little Rock, Arkansas.
[5] University of Arkansas School of Medicine, Little Rock, Arkansas.

TABLE I

Type of Heart Disease	No.	Functional Classification (Therapeutic Class Not Given Here)				
		I	II	III	IV	Unknown
A.S.H.D.	23	0	3	12	7	1
H.C.V.D.	18	1	9	7	1	0
R.H.D.	15	3	4	3	4	1
Luetic Heart Disease	6	0	0	4	2	0
Congenital Heart Disease	2	0	0	1	0	1
Thyrotoxic Heart Disease	3	0	2	1	0	0
Myxedema Heart Disease	1	0	0	0	1	0
Totals	68	4	18	28	15	3

the entire group had values for k_1 which were less than 0.18×10^{-3}.

2. The median k_1 value in this cardiac population was: $k_1=0.36\times10^{-3}$ minute^{-1}, as against a median value in the noncardiac population of: $k_1=0.55\times10^{-3}$.

3. There was no significant preponderance of k_1 values in relation to any functional classification or etiologic group.

4. Thyrotoxic k_1 values were significantly high (greater than 8.8×10^{-3}), whereas in all 65 euthyroid or hypothyroid patients the entire range of k_1 values was: 0 to 1.83×10^{-3}.

5. In the one patient diagnosed clinically as having myxedema, k_1 was 0.18×10^{-3} minute^{-1}.

Renal rate k_2. The noncardiac range for k_2 values has been 0.09 to 3.90×10^{-3} minute^{-1}, with a median value: $k_2=1.3\times10^{-3}$ minute^{-1}. It is probable that without renal disease the lower limit of normal would be about $k_2=0.4\times10^{-3}$.

In the 68 cardiac patients, 66 had a range of values: $k_2=.02$ to 2.1×10^{-3} minute^{-1}. The median value was: $k_2=0.76\times10^{-3}$ minute^{-1}. The two exceptions were (1) a patient with arteriosclerotic heart disease (functional classification not recorded), $k_2=4.9\times10^{-3}$ minute^{-1} and (2) a patient with rheumatic heart disease, classification IV E, $k_2=3.44\times10^{-3}$ minute^{-1}.

Of 44 Class III and IV patients, 27 had values below this median (61 per cent), whereas of 24 Class I and II patients, 7 had values below this median (25 per cent). Thus, k_2 was generally lower in the III and IV groups than in the I and II categories.

RELATIONSHIP OF k VALUES TO NONPROTEIN-NITROGEN PLASMA VALUES

Fifty-seven of the cardiac patients had both nonprotein nitrogen (N.P.N.) as well as k_1 and k_2 determinations.

All but 8 of these had elevated N.P.N. values (greater than 35 mg. per cent).

Thyroidal rate k_1.

1. The 8 patients with normal N.P.N. values may be analyzed as follows: (a) Cardiac functional classification was available on 7, 4 being III or IV, and 3 being I or II. (b) Five of these patients had k_1 values below 1.0×10^{-3}; 2 had k_1 values between 1.0 and 2.0×10^{-3}; and the remaining patient was thyrotoxic with a k_1 value above 8.8×10^{-3}. (c) Of the 5 with k_1 values below 1.0×10^{-3}, 2 had functional classifications of I and II.

2. There were 34 patients with N.P.N. values between 36 and 50 mg. per cent; these may be analyzed as follows: (a) All but 3 of these patients had k_1 values less than 1.0×10^{-3} minute^{-1}, one of these 3 being thyrotoxic. (b) Ten patients in the entire group had cardiac functional classifications of I or II.

3. There were 13 patients with N.P.N. values between 51 and 100 mg. per cent. (a) All but 2 of these had k_1 values less than 1.0×10^{-3} minute^{-1}. (b) Of the 11 of these with known cardiac functional status, only 1 was better than III or IV.

4. There were 3 patients with N.P.N. values greater than 100—all with k_1 less than 1.0×10^{-3} minute^{-1}; 2 of these, however, were in cardiac functional classification II.

5. In all groups, there was a depression of k_1 and preponderance of elevated N.P.N. values—but no correlation between the

extent of elevation of N.P.N. or depression of k_1.

Renal rate k_2. Considering the noncardiac k_2 range as .09 to 3.90×10^{-3} minute^{-1}, 5 patients had k_2 values less than .09; and of these 5, four had N.P.N. values of 67 mg. per cent or greater, 3 being greater than 100 mg. per cent, and the remaining 1 also moderately elevated.

The k_2 values otherwise were also in the lower ranges (below 1.5×10^{-3}) in 44 patients.

There were 7 patients with normal N.P.N. values. These had functional classifications III or IV. Only 2 of these 7 patients had k_2 values exceeding 1.5×10^{-3} minute^{-1}.

There were 8 patients in all with k_2 greater than 1.5×10^{-3} minute^{-1}, but of these only 2 had normal N.P.N. values.

It is thus apparent that no definite relationship has been established in our cardiac patients, except that k_2 tends to be depressed—but not below noncardiac limits—despite the fact that most of our patients had impaired renal function as indicated by elevated N.P.N. values.

Relationship of P.B.I. with k values in cardiac patients (tables II and III)

With the normal population, the values of k_1 followed P.B.I. values fairly closely, in contrast to k_2,—which does not appear to be significantly related.

With the cardiac population tested in this series, it is apparent that both k_1 and k_2 are depressed more than the P.B.I., even to the point of subnormal k_1 values in considerable numbers despite the lack of myxedema clinically.

In the total of 57 patients upon whom both of these values were tabulated:

k_1 correlation with P.B.I.:

There were 2 cases in the hyperthyroid range by both P.B.I., and k_1, and one case hyperthyroid by k_1, with a high normal P.B.I.

There were 11 other values subnormal in relation to k_1, but with normal P.B.I. values and 1 of these had a low k_2 value also. Of these 11, 7 cases had P.B.I. values ranging between 5.6 and 8.0 micrograms per cent.

Although 50 of the 57 patients had k_1 values 0 to 1.0×10^{-3} minute^{-1}, only 32 patients had P.B.I. values less than 5.6 mg. per cent.

k_2 correlation with P.B.I.:

The 2 patients with elevated P.B.I. values in the hyperthyroid range had normal k_2 values.

Of the 6 patients with subnormal P.B.I. values, 2 had k_2 values below normal, and the other 4 low normal values (.09–1.5×10^{-3}).

Table II

Tabulation of N.P.N. in accordance with cardiac functional classification and k_1 values (58 patients)

10^3 k_1	0 to 0.179	0.18 to 1.0	1.1 to 2.0	2.1 to 3.8	73.8	Totals	
per cent mg. N.P.N.							
25 to 35							
I		1				1	
II		1			1	2	
III	2	1				3	8
IV			1			1	
Unknown			1			1	
36 to 50							
I	1					1	
II	2	6	1			9	
III	3	10	1		1	15	34
IV	2	6				8	
Unknown		1				1	
51 to 100							
I							
II		1				1	
III	1	2	2			5	13
IV	2	3				5	
Unknown	1	1				2	
>100							
I							
II		2				2	3
III	1					1	
IV							
Unknown							
Totals	15	35	6		2	58	

TABLE III

TABULATION OF N.P.N. IN ACCORDANCE WITH CARDIAC FUNCTIONAL STATUS AND k_2 VALUES (57 PATIENTS)

10^3 k_2	0 to 0.08	.09 to 1.5	1.6 to 2.5	2.5 to 3.9	3.9	Totals	
per cent mg. N.P.N.							
25 to 35							
I		1				1	
II					1	1	
III		3				3	7
IV				1		1	
Unknown		1				1	
36 to 50		1					
I						1	
II		8	2			10	
III		11	1			12	31
IV	1	6				7	
Unknown		1				1	
51 to 100							
I							
II		1				1	
III		7				7	
IV	1	3	2			6	16
Unknown		1	1			2	
>100							
I							
II	2					2	
III	1					1	3
IV							
Unknown							
Totals	5	44	6	1	1	57	

TABLE IV

TABULATION OF P.B.I. VALUES IN ACCORDANCE WITH k_1

P.B.I.	<3.8	3.8 to 5.5	5.6 to 6.0	6.1 to 8.0	>8.0	Totals
10^3 k_1: 0–0.17	2	4	3	4		13
10^3 k_1: 0.18–1.0	4	19	8	7		37
10^3 k_1: 1.1–2.0		3	0	1		4
10^3 k_1: 2.1–3.8						
10^3 k_1: >3.8				1	2	3
Totals	6	26	11	12	2	57

TABLE V

TABULATION OF P.B.I. VALUES IN ACCORDANCE WITH k_2

P.B.I.	<3.8	3.8 to 5.5	5.6 to 6.0	6.1 to 8.0	>8.0	Totals
10^3 k_2: 0–0.09	2	1	0			3
10^3 k_2: 0.9–1.5	4	22	9	10	1	46
10^3 k_2: 1.6–2.5		2	2	2	1	7
10^3 k_2: 2.5–3.9		1				1
10^3 k_2: >3.9						
Totals	6	26	11	12	2	57

There were no k_2 values above normal, and only 8 values above 1.5×10^{-3}. Of these latter 8, only 2 P.B.I. values were in the high normal range (above 6.0 mg. per cent); and 3 were below 5.5 mg. per cent.

CONCLUSIONS IN RELATION TO k VALUES AND CARDIAC STATUS

1. Clearance rate factors for I^{131} tend to be lower in cardiac patients than in the population at large, with the probable exception of the thyrotoxic cardiac patient where the factors remain elevated.

2. The "hypothyroid zone" for clearance rate factors in the cardiac patients is too extensive to be useful as a diagnostic parameter.

3. These findings may be explained by any or all of the following: (a) Sluggish blood flow through the thyroid gland; (b) retention of iodine in the tissue fluids; (c) depressed thyroidal function in cardiac patients; (d) impaired renal function with resultant increase in subclinical as well as clinical tissue edema, which, in turn, brings about retention of I^{131} in the tissues; (e) diminished renal blood flow producing impaired renal clearance, and increase in tissue fluid space.

CONCLUSION

Special criteria must be utilized in evaluation of thyroidal and renal clearance of I^{131} in patients with cardiac disease. The values tend to be depressed below the

usual normal range for noncardiac patients in a number of patients without clinical myxedema.

Interpretation regarding hyperthyroidism is probably more accurate in cardiac patients using the above diagnostic criteria.

I. Meschan, M.D.
Department of Radiology
Bowman Gray School of Medicine
Winston-Salem 7, North Carolina

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A STUDY OF METHODS FOR INTERSTITIAL IMPLANTATION OF RADIOACTIVE MATERIALS. II. FILAMENTS CONTAINING Y^{90}

By H. C. DUDLEY, PH.D.,* JOSEPH GREENBERG, M.D.,† *and* S. S. SARKISIAN, M.D.‡
U. S. Naval Hospital
ST. ALBANS, NEW YORK

STUDIES carried out on fused germanium oxide needles or filaments containing P^{32} or Au^{198} indicated that these radioactive isotopes could be implanted in tissues, the beta component of their emissions producing marked tissue changes in a more or less circumscribed area.[2,4] However, the filaments were quite brittle, the P^{32} leached to a considerable extent and was carried to other tissues, while the gamma emission of Au^{198} caused excessive radiation exposure to those preparing and handling the filaments. For these reasons and because of experimental and clinical findings which pointed toward the potential usefulness of radioyttrium (Y^{90}) for localized tissue irradiation,[4,8,9] a plastic filament containing Y^{90} has been prepared by extruding from a heated die a mixture of methylcellulose, propyleneglycol and radioactive yttrium (Y^{90}).[3,4]

Since completing the studies as outlined herein, there have appeared descriptions of techniques making use of 0.8 mm. ceramic spheres containing Y_2O_3 as well as studies of the effects on the cerebral cortex of cats after implantation of a gelatin sponge impregnated with Y^{90}.[1,7]

In the present report are given (a) additional details of the preparation of flexible filaments containing Y^{90} and (b) the tissue response in rabbits and dogs in which the filaments had been implanted. Details include results of microscopic examination of tissue to 90 days postimplantation.

MATERIALS AND METHODS

Preparation of Filaments. Previously it was shown that a tissue-soluble plastic filament containing yttrium oxide could be prepared by extruding a mixture of previously activated Y_2O_3 ($Y^{89}n,\gamma\ Y^{90}$), powdered methylcellulose and propyleneglycol. Details of this procedure have been given earlier.[3,4]

The filaments prepared by this method were found quite useful in the 1.1 mm. diameter size, and it is this preparation which has been used in the majority of the animal experiments described herein. The proportion of Y_2O_3 may be varied within limits, depending on the specific activity of the oxide; however, in these studies the filament contained 1,000–1,800 microcuries/linear cm. (finished form, 30–35 per cent Y_2O_3).

The flexibility of the filaments may be increased both by reducing the cross section, and decreasing the oxide content. Therefore high specific activity Y^{90} may be utilized to accomplish this result. A quite flexible suture-like filament of good tensile strength has been prepared and used in one series of the animal studies. The tissue response was indistinguishable from that produced by the larger, more rigid filaments if the Y^{90} content (as μc/linear cm.) was the same in both.

By selectively leaching an exchange resin column containing radiostrontium (Sr^{90}) the first-step decay product, Y^{90}, may be

* Captain, MSC, USN.
† Lieutenant, MC, USNR.
‡ Captain, MC, USN.
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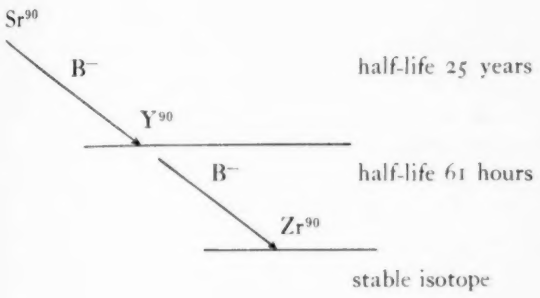
obtained essentially free of the parent material:



The use of a small amount of "carrier," stable Y^{89}, increases the recoverable yield of this process. The material used in certain of our studies was obtained from the Abbott Laboratories, which supplied the Y^{90} prepared by this general method.

Approximately 150 millicuries (mc) of Y^{90}, in acid solution with the carrier as furnished, was placed in a platinum crucible or dish, and 100 mg. pulverized Y_2O_3 added. A drop or two of ammonium hydroxide was then added (to pH 8.0), and the dish brought to dryness without spattering. After drying, the dish was heated in an electric furnace to a dull red to decompose and eliminate the ammonium complex. On cooling, the oxide was repulverized with a metal spatula and intimately mixed with 500 mg. powdered methylcellulose (Dow, #2606, 50 cps.). To this mixture was added 1 ml. of propyleneglycol. The mixture was then stirred and allowed to stand from 10 to 15 minutes. The dough-like mass was placed in a heated press and extruded through a die of 1.04 mm. diameter.[4] The soft filament was placed in a drying oven at 110° C. for 10 to 12 hours, resulting in a dense, flexible suture-like filament of good tensile strength which could be threaded in a standard suturing needle.

Safety Precautions. In the handling of 100–200 mc Y^{90} and in the preparation of the filaments, certain important safety precautions must be observed to prevent overexposure to radiation. Although Y^{90} emits only beta particles, Bremsstrahlung (soft secondary gamma) is produced when the high energy beta rays (max. 2.2 mev.) are absorbed by the oxide and the containers. Therefore, the gamma exposure to the hands is in excess of 2,000 milliroentgens (mr)/hr. at 0.3 meters from an unshielded 200 mc Y^{90} source. The use of tongs and forceps to handle the containers is mandatory. Leaded glass serves as an excellent shield to reduce excessive whole body exposure.

By developing the technique first with inert materials, learning rapid manipulation, the use of tongs and suitable shields, exposure of the hands during the entire preparation procedure has been kept to less than 200 mr. Whole body exposure did not exceed 50 mr.

No significant exposure results from the use of these filaments if they are manipulated with forceps or tongs. Once implanted, there is little radiation observable at the skin surface, so that radiation exposure of attending personnel is negligible. Only minute amounts of Y^{90} appear in the urine or feces following implantation of these filaments so that excreta may be disposed of in the usual manner.

ANIMAL STUDIES

Rabbits. Three series of rabbits, 8 animals in each series, were given subcutaneous local anesthesia (procaine) over the abdominal wall. Two 5 cm. lengths of filament prepared by one of the methods described previously were implanted in each animal in the muscle sheath between the dermis and the peritoneum. Implantation was accomplished by making two small incisions on each side of the abdomen, producing a sinus with a stilet, and drawing the filament through this opening with smooth nose forceps.

In Series 1, nonradioactive filaments containing 32 per cent Y_2O_3 (1.1 mm. diameter) were implanted and 2 animals killed on the second, seventh, fourteenth and thirtieth days after implanation. Gross examination of all animals was made, and

tissue taken for histologic study from the 7 and 30 day animals.

In Series II, radioactive filaments (1.1 mm. diameter) were prepared with Y_2O_3 previously rendered radioactive by neutron irradiation in the Brookhaven reactor (32 per cent Y_2O_3, 1,800 μc Y^{90}/linear cm.). The filaments were placed into the abdominal wall of 8 rabbits as indicated above, and 2 animals killed on the seventh, fourteenth, thirtieth and sixtieth days postimplantation. Tissues were taken at the time of the gross examination for more detailed study from the 7, 14, and 30 day animals. The liver, spleen, and kidneys of the animals killed on the seventh and fourteenth days were removed, sectioned, and representative samples taken. These were dried and beta counts made of samples mounted in aluminum planchets in order to estimate the degree of translocation of the Y^{90} due to the mobility of the smaller Y_2O_3 particles.

Series III duplicated the procedure as outlined above for Series II; however, in this case the filaments were formed with Y^{90}, derived from Sr^{90}, as described above. The filament was quite flexible (0.7 mm. diameter) containing 5–6 per cent Y_2O_3 and 1,200 μc Y^{90}/linear cm. Detailed histologic study was made of the animals sacrificed on the seventh and fourteenth day postimplantation.

In each rabbit sacrificed during these studies, the abdominal wall was excised and the dermis stripped away. The area was grossly examined, and the tissue fixed in 5 per cent formalin. After paraffin imbedding, representative sections were stained and examined microscopically.

Dogs. Mongrel dogs were used in the study of effects of Y^{90} filaments containing 30–35 per cent Y_2O_3 with 1,200–1,800 μc Y^{90}/linear cm. Under general pentothal anesthesia Y^{90} filaments were implanted in the liver and lung of one dog and the animal sacrificed 30 days later to study the changes induced in these normal tissues.

Under general pentothal anesthesia Y^{90} filaments of various lengths have been implanted in the posterior parietal lobes of 6 dogs, and the resulting changes studied at intervals up to 90 days postimplantation. Control animals consisted of 1 dog which underwent this surgical procedure but with no filament implant, and 1 in which there was a parietal implant of a 1.5 cm. length of 1.1 mm. diameter filament containing 32 per cent nonradioactive Y_2O_3. Uneventful recovery was made in both controls.

At death, or at time of sacrifice, selected tissues were removed, examined grossly, and color photographed. In the case of the cerebral implants, the brain was removed *in toto*, and gross serial sections made. The tissues were preserved in 5 per cent formalin, paraffin blocked, stained, and microscopically examined.

RESULTS

Implantation of methylcellulose filaments containing nonradioactive Y_2O_3 into the abdominal wall of rabbits produced no grossly observable change which could not be explained by the trauma of the procedure. At 48 hours the filament had disintegrated leaving a line of yellowish Y_2O_3. By 14 days the area had healed and could not be located at autopsy except by an occasional clump of the oxide. Examination of the brain of a dog 60 days following implantation of the nonradioactive filament into a parietal lobe, showed little or no residual effect at the site or in adjacent tissues.

When filaments containing 1,200–1,800 microcuries Y^{90} per linear cm. were implanted in the abdominal wall of rabbits, there was produced within 7 days a sharply defined zone of necrosis induced by the beta emission of the Y^{90}. This zone was cylindrical, 10–12 mm. in diameter, extending 5 mm. beyond each end of the filament. With time this necrotic area underwent progressive change so that at 30 days postimplantation the area was essentially healed, leaving a dense, white scar-like structure 10 mm. in diameter. The rabbits so treated gave no indication

of pain and remained in excellent condition. Examination of excreta and selected tissues indicated no significant translocation of the Y^{90}.

Implantation of Y^{90} filaments into a posterior parietal lobe of dogs caused death in 2 animals on the seventh and ninth days, respectively, with symptoms indicative of intracranial pressure. In these animals 4 to 5 cm. of filament was used in each, which apparently caused rapid destruction of a large part of the lobe with resultant cerebral edema. Four other dogs, into which smaller amounts (0.5–2.0 cm.) of filament were implanted, survived and one each was sacrificed on the ninth, thirtieth, sixtieth and ninetieth day postimplantation. In 3 of these animals there appeared symptoms of varying degrees of cerebral pressure, including in 2 a partial temporary blindness. However, these symptoms had cleared by the fourteenth day and thereafter recovery was uneventful. Refer to the pathologic section below for further details of gross and histologic description.

PATHOLOGY

Controls.

Rabbit X13–55. Subcutaneous methylcellulose filament implant 7 days postoperatively. The gross examination of the subcutaneous tissue revealed an area of hemorrhage which was undergoing early organization as evidenced by friability and a dark brown color. Histologically, the tissue revealed a nonspecific granulomatous response with foreign body giant cells, inflammatory cells and pigment-laden phagocytes. There was no evidence of implanted material.

Rabbit X16–55. Subcutaneous implant of methylcellulose filament containing yttrium oxide (Y_2O_3), nonradioactive, 7 days postoperatively. The gross examination of the subcutaneous tissue revealed an area of hemorrhage, edema and dark brown pigmentation. Histologic examination revealed intercellular tissue edema and nonspecific foreign body granuloma response. There was also an accumulation of brown irregular crystalline material interpreted as deposited Y_2O_3.

Rabbit X9–55. Subcutaneous implant of methylcellulose filament containing yttrium oxide (Y_2O_3), nonradioactive, 35 days postoperatively. The gross examination of the subcutaneous tissue revealed a pigmented scar. The histologic examination revealed a fibrous scar with deposited Y_2O_3 in the form of brown irregular cystals.

Dog X9–56. Intracranial implant (right parietal area) of methylcellulose filament containing yttrium oxide (Y_2O_3), nonradioactive, 60 days postoperatively. The gross examination of the brain revealed a depressed scar in the right parietal cortex. Sectioning of the brain revealed a slightly pigmented brown 1 mm. linear area extending for a distance of 2.5 cm. into the white substance. The histologic examination revealed a local gliosis with brown pigment deposition. There was no inflammatory infiltration.

Pertinent conclusions drawn from these test cases are:

1. Methylcellulose filaments are absorbed completely with slight local tissue irritation.
2. Y_2O_3 is not absorbed nor phagocytized but remains *in situ*.

Y^{90} Implants.

Rabbit X7–55. Subcutaneous implant of radioactive yttrium oxide (Y^{90}) in methylcellulose filament, 7 days postoperatively. The gross examination of the subcutaneous tissue revealed local edema, hemorrhage and necrosis. Histologic examination revealed an area of marked tissue necrosis with acute inflammatory infiltration and brown pigment deposition (Fig. 1).

Rabbit X8–55. Subcutaneous implant of radioactive yttrium (Y^{90}) in methylcellulose filament, 14 days postoperatively. The gross examination of the subcutaneous tissue revealed a progression of the zone of necrosis which was seen in the previous animal with a more definite demarcation from the adjacent tissue. Histologic examination revealed local tissue necrosis, round

FIG. 1. Rabbit X7–55. Seven day radioactive yttrium implant in subcutaneous tissue (80×).

cell infiltration and numerous eosinophils. Brown Y_2O_3 deposit was surrounded by an area devoid of any cellular structures.

Rabbit X7–56. Subcutaneous implant of radioactive yttrium oxide (Y^{90}) in methylcellulose filament, 30 days postoperatively. The gross examination revealed an area of soft white scar tissue. Histologically the tissue revealed an area of minimal tissue response with fibrosis.

Dog X18–55. Brain implant of radioactive yttrium oxide (Y^{90}) in methylcellulose filament in the right parietal area, 9 days postimplantation. The gross examination revealed a 2 cm. area of hemorrhage on the cortical surface. Serial sections of the brain revealed a hemorrhagic linear lesion 1.5 cm. wide and extending from the brain cortex into the white substance for a distance of 4.5 cm. (Fig. 2). Histologic examination revealed an area of acute inflammatory infiltration, hemorrhage and tissue destruction centered around the deposited brown particles of yttrium oxide (Fig. 3).

Dog X5–56. Brain implant of radioactive yttrium oxide (Y^{90}) in methylcellulose filament in the right parietal area for 19 days. The gross examination revealed an area of depression and yellow brown pigmentation 1 cm. in diameter. Serial sections revealed a similar linear lesion 3 cm. in length which extended into the white substance of the brain (Fig. 4). The histologic examination revealed an area of tissue ne-

FIG. 2. Dog X18–55. Nine day radioactive yttrium implant in brain (gross view).

FIG. 3. Dog X18–55. Nine day radioactive yttrium implant in brain (160×).

crosis and numerous phagocytic cells around the area. There was no evidence of recent hemorrhage (Fig. 5).

Dog X8–56. Brain implant of radioactive yttrium oxide (Y^{90}) in methylcellulose filament in the right parietal area for 60 days. The gross examination of the brain revealed a 1 cm. depressed yellow scar. On serial sectioning of the brain, the scar extended for a depth of 2 cm. into the brain substance. The adjacent brain tissue was normal (Fig. 6). The histologic examination of the brain section revealed a sharply circumscribed area of brain gliosis with minimal inflammatory infiltration. In the center of this area there was deposited a brown pigmented crystalline material which represented the implant of yttrium oxide (Fig. 6). The adjacent brain tissue revealed a narrow zone of petechial hemorrhage (Fig. 7).

Dog X10–56. Brain implant of radioactive yttrium oxide (Y^{90}) in methylcellulose filament in the right parietal area for 90 days. The gross examination of the brain revealed a 0.5 cm. slight depression

Fig. 5. Dog X5–56. Nineteen day yttrium implant in brain (160×).

Fig. 4. Dog X5–56. Nineteen day yttrium implant in brain (15×).

Fig. 6. Dog X8–56. Sixty day yttrium implant in brain (15×).

FIG. 7. Dog X8–56. Sixty day yttrium implant in brain (160×).

on the cortical gray surface. Serial sectioning revealed an area of cortical gray substance to be absent. The histologic examination revealed an area of scar formation with no abnormality of the adjacent brain tissue. Remaining yttrium oxide pigment was seen (Fig. 8).

Dog X 10–55. Liver implant of radioactive yttrium oxide (Y^{90}) in methylcellulose filament after 35 days. The gross examination of the liver revealed a 2 cm. sharply demarcated circular area of liver necrosis which was firm, reddish-brown in color and adjacent to the liver capsule (Fig. 9). The histologic examination revealed a sharply defined area of liver necrosis with scar formation and minimal inflammatory response. The liver scar ended abruptly and normal appearing liver cells were adjacent to this zone (Fig. 10).

Pertinent conclusions demonstrated in these cases are:

1. The radioactive yttrium oxide as used in this series of animals causes sharply demarcated local tissue necrosis.

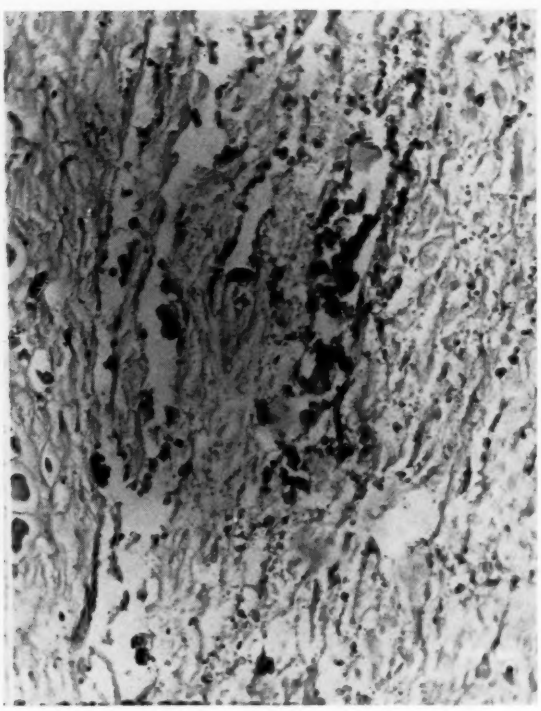


FIG. 8. Dog X10–56. Ninety day yttrium implant in brain (160×).

FIG. 9. Dog X10–55. Thirty-five day yttrium implant in liver (15×).

2. Adjacent tissues beyond the area of radioactive effect change abruptly into normal appearing tissue histologically. In effect, the intermediate zone of cells showing partial changes to radioactivity is on the order of four to ten cell layers thick.
3. Complete healing of the tissue involved with stable scar formation can be demonstrated.

DISCUSSION

The utilization of tissue-soluble filaments containing an insoluble radioactive material offers to the physiologist a method of destroying discrete areas in the central nervous system for the study of nerve function. The advantage to be derived from Y^{90} is that there appears to be little or no foreign body reaction induced by the Y_2O_3 remaining after solution of the methylcellulose matrix. No additional surgical trauma is necessary for removal of the radioactive source as in the case with long life gamma emitters, *i.e.*, Ra, Rn, Co^{60}.

Ablation of glandular tissue may be accomplished by implantation of small segments of filaments within the gland. Since success of many current procedures depends on complete surgical removal of hormone-producing tissue, implantation of sufficient Y^{90} filament to cause its complete *in situ* destruction can be accomplished with a minimum of surgical trauma.

Total adrenalectomy or hypophysectomy by the parapharyngeal approach appear to be procedures which lend themselves to the use of Y^{90} filaments.

The effects on tissue of filaments emitting only beta particles are markedly different from those produced by gamma or roentgen radiation. It is an "all or none" effect, there being complete cellular destruction adjacent to the filament, with the zone of transition to normal tissue approximately 50 microns in width. By reducing the Y^{90} concentration to less than 500 microcuries per linear centimeter, the diameter of the primary action can be held to a few millimeters. At a concentration of 1,000–1,800 μc/linear cm. the tissue destruction extends to the maximum diameter obtainable (10–12 mm.). Thus, by adjusting the Y^{90} content of the filament it is possible to ablate a small volume of tissue, or with the high concentrations and multiple implants, to destroy any desired volume.

Fig. 10. Dog X10–55. Thirty-five day yttrium implant in liver (160×).

Localized destruction of tissue within discrete neoplastic lesions can be accomplished by the use of the Y^{90} filaments described herein. This phase of the study is now underway and clinical findings will be reported when sufficient data have been obtained. Preliminary results indicate the usefulness of this approach in selected cases.

SUMMARY AND CONCLUSIONS

The therapeutic applications of the newer forms of induced radioactivity follow much the same modes of procedure as utilized during the past 4 decades for roentgen rays, radium or radon. One of the newer approaches is the total destruction of tissues by intense beta radiation, making possible closely circumscribed effects.

Flexible, tissue-soluble, plastic filaments containing radioactive yttrium (Y^{90}) have

been prepared. Microscopic studies of the tissues following subcutaneous implantation in rabbits have shown that nonactivated filaments (methylcellulose 32 per cent Y_2O_3) are absorbed in 7 days, only a localized granuloma with fibrosis remaining. With the filament containing Y^{90} the tissue response 7 days postimplantation was that of local tissue necrosis and sterile abscess formation; by 35 days all that remains is an aseptic necrosis with zonal fibrosis.

Examination of the brains of dogs receiving the Y^{90} filaments has shown that in 7 days there was local tissue necrobiosis; by 19 days there was some additional extension of the zone of necrosis with early stabilization of the lesion; by 35 days there was a sharply delimited area of necrobiosis; at 90 days the repair process was complete.

Use of radioactive filaments which are soluble in tissues, and therefore do not necessitate later removal, offers a convenient means of implanting radioactive materials for the (a) destruction of discrete areas in the central nervous system in neurologic research, (b) destruction of glandular tissue, *i.e.*, adrenalectomy, hypophysectomy, (c) localized desttuction of neoplastic lesions, and (d) destruction of blood supply of a lesion by marked local scarification.

As a result of these studies it is concluded that where it is desirable to produce closely circumscribed areas of tissue destruction, filaments similar to these described here containing radioyttrium (Y^{90}) are worthy of further study. Controlled use of this modality in the treatment of localized malignancies in humans is indicated and is currently under way at this hospital.

H. C. Dudley, Capt., MSC, USN
U. S. Naval Hospital
St. Albans, Long Island 25, New York

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THE PRESENT RADIOISOTOPE TEACHING PROGRAM FOR MEDICAL STUDENTS IN THE UNITED STATES*

By B. V. A. LOW-BEER,† M.D., *and* REYNOLD F. BROWN, M.D.
SAN FRANCISCO, CALIFORNIA

THE increasing difficulties of medical schools in trying to orient the student in the broad expanse of modern medical knowledge are well illustrated by the subject of radioisotopes. To evaluate the present status of teaching this particular subject, a questionnaire was sent on April 14, 1955, to the deans of 80 medical schools in the United States. The questions asked are given herewith, together with a listing of the number of schools replying and how they replied.

A. Is this subject formally taught in your medical school as:

	Yes	*No*	*No Answer*
1. A course in itself?	10	64	6
2. Integrated with other courses?	70	2	8

B. How many class hours are devoted to the subject?

Number of Schools	*Number of Hours for Four-Year Term*
11	No Answer
10	0
15	1–5
16	6–10
11	11–15
12	16–25
5	25–50

Of the above schools responding, some only gave 1–5, 6–10, etc., hours of instruction during the entire 4-year period. Following is a breakdown of the number of hours instruction given by class:

Hours	*Freshmen*	*Sophomores*	*Juniors*	*Seniors*
	No. of Schools			
1–5	27	28	34	25
6–10	4	3	7	7
11–15	6	4	4	3
16–25	0	1	1	1

C. Is this subject taught in conjunction with and time allotted to:

	No. of Schools		*No. of Schools*
Pathology	14	Pharmacology	2
Internal Medicine	50	Biochemistry	7
Surgery	25	Physiology	3
Radiology	46		

D. If this subject is not included in the present teaching program, is it your and your faculty's intention to introduce it as an integral part of the curriculum?

Yes	*No*	*No Answer*
15	18	47

E. Should the teaching include the use of radioisotopes for:

	Yes	*No*	*No Answer*
1. Tracer studies as investigative tools?	70	0	10
2. Diagnostic laboratory tests?	70	0	10
3. Therapeutic uses?	69	1	10

F. Should such a course include lectures with laboratory exercises or lectures only?

Lectures Only	*Lectures and Laboratory*	*No Answer*
10	63	7

G. In your opinion, should this subject be presented only in its relation to diagnostic and therapeutic radiology, or should it encompass all medical uses of atomic energy (*i.e.*, industrial medicine) and the dangers of ionizing radiations in peace and war?

All Uses	*Radiology Only*	*No Answer*
63	10	7

H. If the subject is formally taught in your school, do you have a syllabus available?

Yes	*No*	*No Answer*
3	70	7

Some instruction in radioisotopes is given in nearly all medical schools, usually integrated into the subjects already organized in the curriculum. It must be

* From the Department of Radiology, University of California School of Medicine, San Francisco, California.
† Deceased.

emphasized that this material is of a general nature, and is not designed to give proficiency in use but orientation in the field of application. The number of hours is variable due to the manner of integration. Of the 80 schools answering the questionnaire: 42 give 15 hours or less of instruction, 10 reported no hours of instruction, and 11 gave no answer to the question. In some 14 schools, they are unable to designate any particular hours devoted to the subject, but do state that it is integrated into the curriculum.

There is continued activity and discussion of the need for additional training in radiology in all aspects, and the trend is definitely to increase the hours devoted to this subject, including the aspects of radiation hazards in national defense. Therefore, we can expect increasing effort in presenting information to the students. This does not mean that when students graduate they will be proficient in the use of radioisotopes, since any undergraduate course possible within the present curriculum would fall far short of the time presently considered as the minimum for training and education sufficient for the intelligent use of radioisotopes in humans. It does mean, however, that students will learn the uses and limitations of radioisotopes. It also underscores the fact that the teaching of their clinical use will remain at the postgraduate level for the foreseeable future in all institutions where it is believed that at least 250 hours is the minimum time needed to train physicians already well informed in basic science, and that, perhaps, 500 hours is a more realistic program for such training in the clinical use of radioisotopes. Postgraduate courses of a few days' duration should be considered as orientation courses only. The growth of postgraduate training has been rapid and is continuing to expand, so that nearly all institutions equipped to teach will be training more physicians, resulting in the availability of radioisotopes to any patient requiring their application.

Reynold F. Brown, M.D.
University of California Medical Center
San Francisco 22, California

THE RADIATION DISTRIBUTION AND DOSE SPECIFICATION IN VOLUME IMPLANTS OF RADIOACTIVE SEEDS*

By R. J. SHALEK, M. A. STOVALL, *and* V. A. SAMPIERE
HOUSTON, TEXAS

WITH the gold grain gun[3] or with nylon tube techniques,[2] it is practical procedure to implant volumes of tissue with radioactive seeds. By far, the most convenient arrangement of the seeds is the placing of equally active seeds at nominal spacings (say, one centimeter) thus achieving a uniform distribution of sources in accord with the Quimby system but not with the Paterson-Parker system, which recommends a definite relationship between the peripheral and the core sources. In an institution where the interstitial radium work follows the Paterson-Parker system, it is necessary to understand the dosage relationship between the seed volumes and Paterson-Parker needle volumes in order that there may be a continuity of clinical results related to dose specification. The three calculation possibilities for the seed volumes are (a) the Quimby tables,[1] (b) the Paterson-Parker tables,[4] and (c) new tables. In this instance the alternative desired is that which is most consistent with Paterson-Parker needle volumes. One is tempted to try to employ (a) and (b) interchangeably, using the system which best fits a particular distribution of sources. This practice is unsound and can lead to serious confusion in dose specification since the difference in calculated value by the two methods for an implant may amount to 35 per cent or more. Each system is self consistent. The disagreement arises partly from the difference in the distribution of sources and partly from the position of dose specification as will be discussed later. A therapist accustomed to a certain result for a given dose in one system should not expect the same result for the same dose in the other system. Quimby and Castro[5] have considered the use of Paterson-Parker tables for distributions of radium needles other than that specified in the Manchester system. They concluded that some variation in needle distribution was permitted within the Manchester system. The present study is an extension of that work to volumes implanted with radioactive seeds.

CALCULATIONS AND EXPERIMENTAL RESULTS

The Radiation Distribution in the Volumes. The seed volumes considered were cubes 1 cm., 3 cm., and 5 cm. on a side with seeds located on a 1 cm. cubic lattice. Spheres were formed from cubes by the removal of the corner and edge seeds. In Figure 1 are shown the configurations of seeds and needles taken for comparison together with the choice of the "lowline"; that is, the line which includes the minimum dose rate for a given distance from the center. For the cubes the lowline was taken to originate at the center of the cube and pass through the center of a face; for the needle volumes the lowline is in a plane perpendicular to the needles at their centers. The dosage to various points along the lowlines for the seed volumes was calculated considering the seeds as point sources and allowing for no radiation absorption in the tissue. The relative doses so calculated were confirmed by film measurements with radioactive gold seeds.[7] The seeds, selected for uniform activity, were supported 1 cm. apart on 1 cm. slabs of mix D wax, and type A film was exposed in a plane dividing the volume midway between two planes of seeds. In Figure 2 is shown the experimental arrange-

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From the University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Presented at the Thirty-eighth Annual Meeting of the American Radium Society, Houston, Texas, April 9–11, 1956.

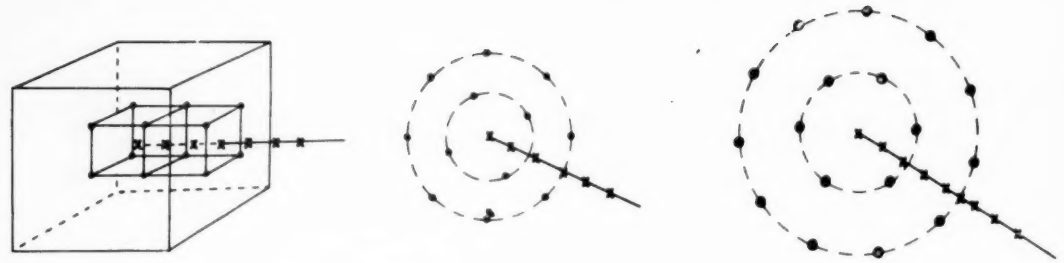
3 X 3 CM CUBE
1 CM CUBIC LATTICE
64 SEEDS (12 SHOWN)
P & P CYLINDER
LENGTH 3 CM
RIND, 8 NEEDLES, R = 1.5 CM
CORE, 4 NEEDLES, R = 0.75 CM
CENTER SECTION,
PERPENDICULAR TO AXIS
P & P CYLINDER
LENGTH 4.5 CM
RIND, 11 NEEDLES, R = 2.25 CM
CORE, 6 NEEDLES, R = 1.0 CM
CENTER SECTION,
PERPENDICULAR TO AXIS

FIG. 1. The arrangement of the sources for calculation and the choice of the lowline.

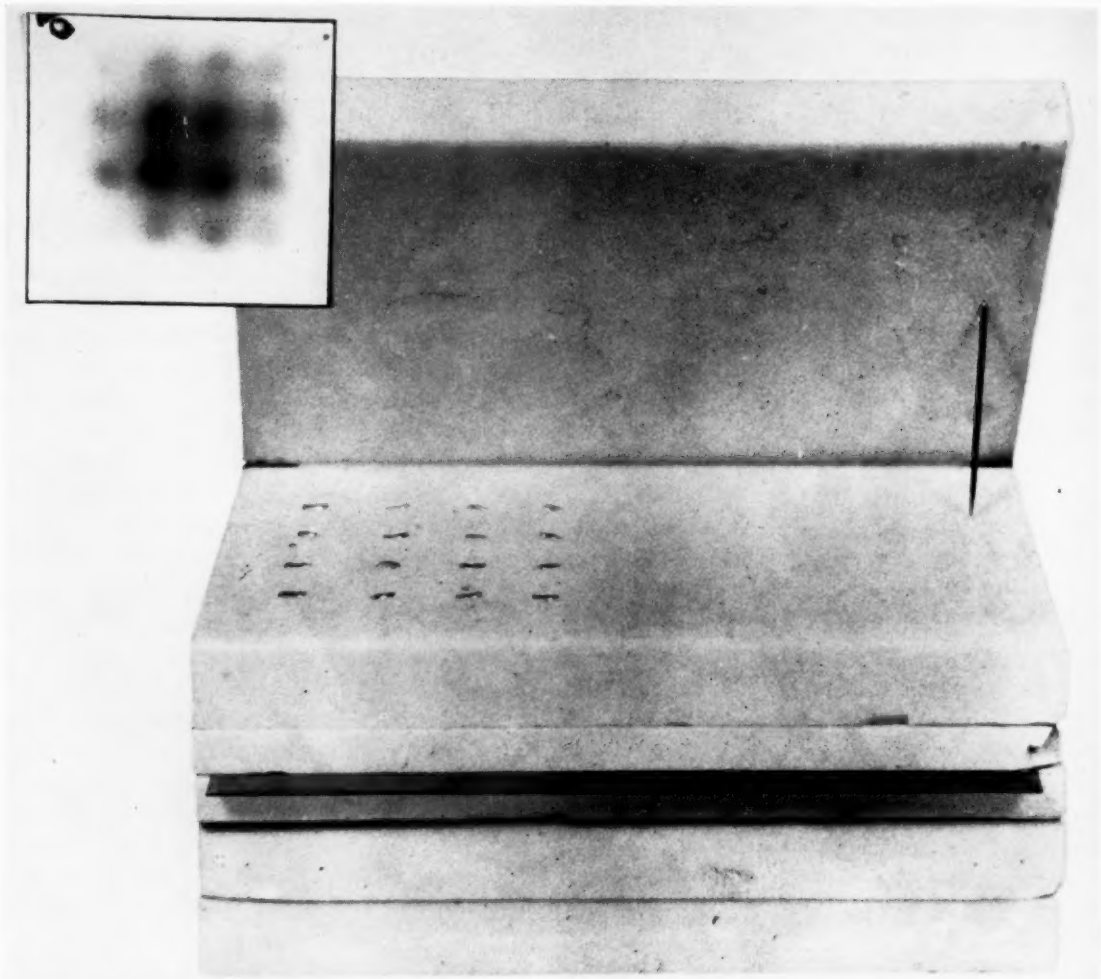

FIG. 2. Experimental arrangement. Sources are held in a 1 cm. cubic lattice by slabs of mix D wax, and type A film is exposed midway between two planes of seeds. In the inset is shown the film for a $3 \times 3 \times 3$ cm. cube.

ment together with an exposed film. For the conversion of film density to dose, a response curve for the film was derived from exposures with the same sources for varying lengths of time. In Figure 3 *A* it is seen that the relative dose obtained along a lowline by calculation agrees with that measured on the film.

The value of the dose rate calculated at the center of the cubes agreed to within 6 per cent with that measured by scintillation methods with a small anthracene crystal. A slender scintillation probe, 5 mm. in diameter, was admitted by a hole to the center of the wax system supporting the seeds. Radium standardization was employed. It was concluded that the calculations gave valid values, both for the relative and the quantitative dose. The discussions that follow are for calculations only.

In Figure 3, *B*, *C* and *D* are shown the calculated relative dose along a lowline for the needle cylinders, the seed cubes and the seed spheres. The arrows indicate the surface of the volume; for the cylinders the circle of implantation is the surface, for the cubes the center of the face is the surface, and for the spheres the average distance of the peripheral seeds from the center was taken as the surface. It is seen that the relative radiation distributions are similar. For the spheres the chosen lowline does pass through the point of minimum dose on the surface. For the cubes the point of minimum dose on the surface is near a corner and, thus, not on the lowline shown in the graphs. The ratios of the

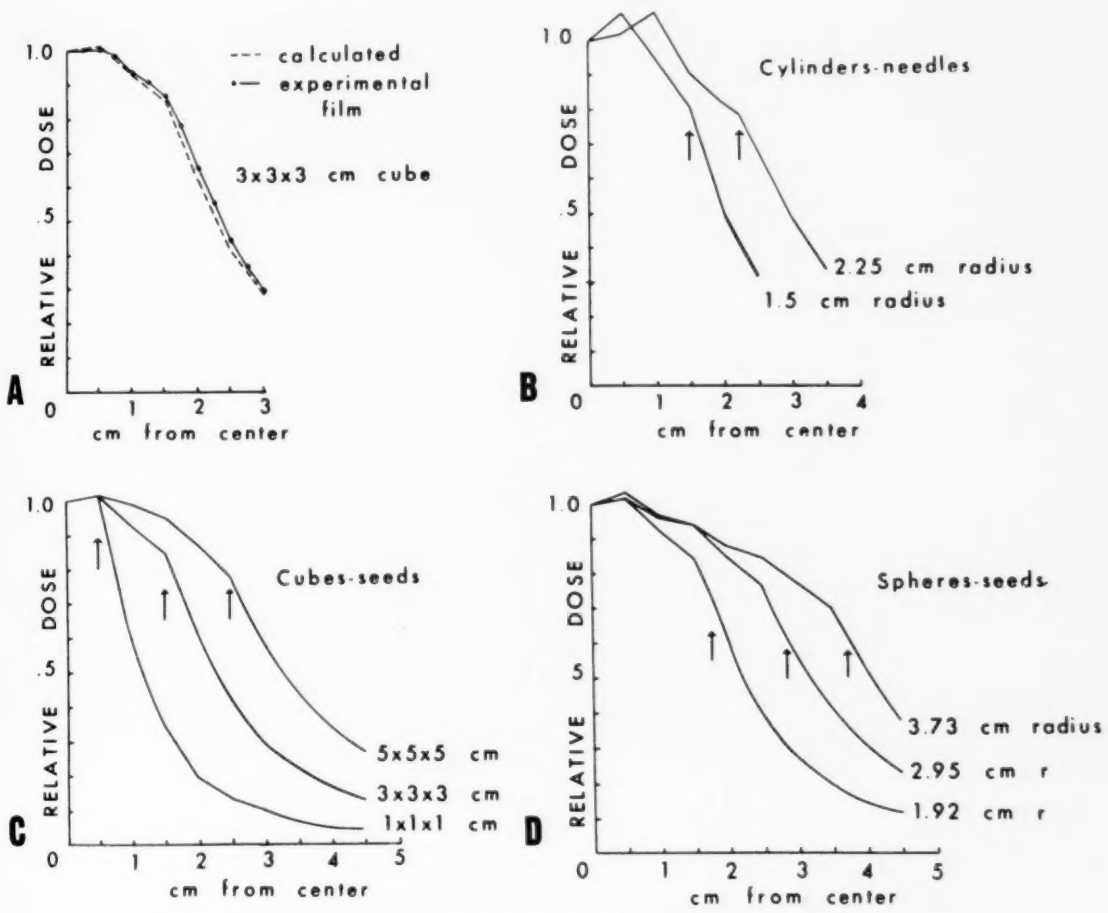

FIG. 3. (*A*, *B*, *C* and *D*) Relative dose from the center outward on a lowline.

lowest surface dose to the center dose are summarized in Column A, Table I for the cases where comparison is possible. For the cubes this ratio varies from 0.61 to 1.00 and for the spheres it is about 0.62. The Paterson-Parker cylinders chosen for comparison give a surface to center ratio of 0.80. In general, as stated by Parker, the surface to center ratio for Paterson-Parker cylinders is about 0.72. Thus, the variation in dose from the center to surface of a seed volume implanted on a 1 cm. cubic lattice is somewhat greater than across a Paterson-Parker needle implant.

Dose Specification and Milligram-Hours per 1,000 r. The information for the volumes considered is summarized in Table I. Following the practice of Paterson and Parker, the net minimum dose rate is 10 per cent above the absolute minimum value

TABLE I

SUMMARY OF CALCULATIONS

Type Implant	*A* Ratio, Surface of Implant to Center	*B* Net Minimum 1 mc/seed* r/hr.	*C* Volume of Implant cm.^{3}	*D* *mg. hr./1,000 r	*E* Millicurie Equivalent of Radon* for Each Permanent Seed for 7,000 r
1×1×1 cm. cube, 8 seeds	1.00	98.7	1.00	80.9	.53
2×2×2 cm. cube, 27 seeds		144	8.0	188	.36
3×3×3 cm. cube, 64 seeds	.75	177	27.0	362	.30
4×4×4 cm. cube, 125 seeds		206	64	609	.25
5×5×5 cm. cube, 216 seeds	.61	232	125	932	.23
6×6×6 cm. cube, 343 seeds		256	216	1340	.21
1.28 cm. radius sphere, 19 seeds		97.8	8.8	194	.54
1.92 cm. radius sphere, 56 seeds	.64	144	29.5	391	.36
2.30 cm. radius sphere, 81 seeds		179	51.0	452	.29
2.95 cm. radius sphere, 160 seeds	.60	205	107	780	.26
3.73 cm. radius sphere, 288 seeds	.61	256	217	1120	.20

Paterson-Parker Cylinders	Ratio, Surface of Implant to Center
Length—3 cm. Rind—8 needles, 1.5 cm. radius Core—4 needles, 0.75 cm. radius	.81
Uncrossed Length = 4.5 cm. Rind—11 needles, 2.25 cm. Core—6 needles, 1 cm. radius	.79

* 0.5 mm. Pt filtration.

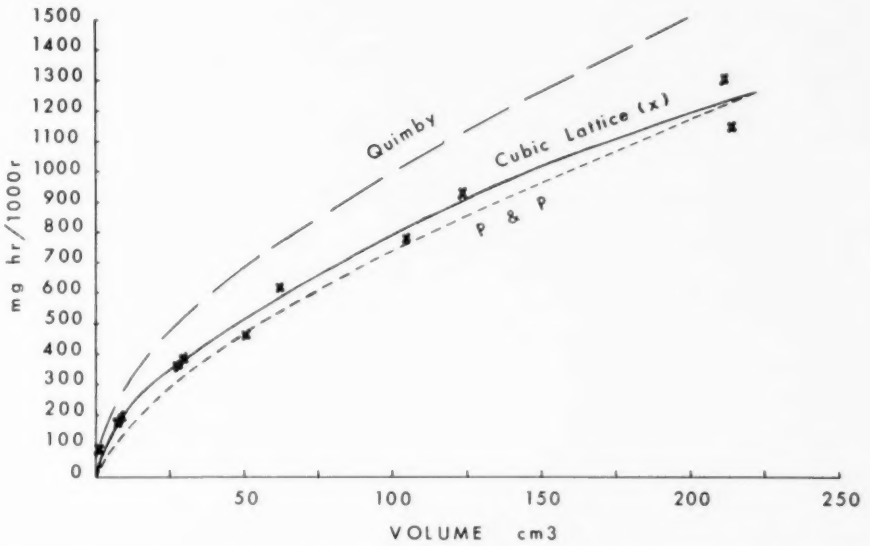

FIG. 4. Mg.-hr./1,000 r versus volume of the implant. The solid line is the average through the new points (x). The curves plotted from the Quimby and the Paterson-Parker tables are shown for comparison.

and is the dose rate used for determining the mg.-hr./1,000 r for the particular cases. In Figure 4 are plotted mg.-hr./1,000 r versus volume as determined from the calculations and the Quimby and the Paterson-Parker tables. It is seen that the new seed curve approximates the Paterson and Parker curve. However, at small volumes, the percentage difference may be considerable as shown in Table II, but above 100 cm.^{3} the differences are less than 5 per cent. In Table III are given the mg.-hr./1,000 r for the seed volumes from 1 to 100 cm.^{3}; above 100 cm.^{3} the Paterson-Parker tables are valid for the seed volumes implanted on a 1 cm. cubic lattice.

It is believed that the differences between the Quimby tables and the Paterson-Parker tables are partly accounted for by the difference in source distribution and partly by the position of dose specification. The Paterson-Parker tables are constructed upon the basis of specifying the dose which is 10 per cent above the absolute minimum and is thus located several millimeters inside the periphery of the volume; the Quimby system specifies the minimum surface dose. Thus, for a given dose specification a larger dose is delivered to the patient with the Quimby system than with the Paterson-Parker system.

One final problem is the activity that is

TABLE II

COMPARISON OF SEED CALCULATIONS WITH PATERSON-PARKER TABLES

Volume, cm.^{3}	Paterson-Parker, mg. hr./1,000 r	Seed Calculations, mg. hr./1,000 r	Seed, mg. hr./1,000 r / Paterson-Parker, mg. hr./1,000 r
5	99.7	150	1.50
10	158.3	210	1.32
25	292	345	1.18
40	399	442	1.11
50	463	502	1.08
100	735	772	1.05
200	1166	1172	1.01

TABLE III

VOLUME IMPLANTS OF RADIOACTIVE SEEDS

Volume in Cubic Centimeters	*mg. hr./1,000 r
1	80.9
2	102
3	118
4	132
5	142
10	209
15	263
20	309
25	344
30	379
40	442
50	502
60	560
70	616
80	670
90	723
100	772

Above 100 cm.^{3}, Paterson and Parker volume tables are valid for seed volumes implanted on a 1 cm. cubic lattice.

* Calculated for radon with a filtration of 0.5 mm. Pt; corrections should be made for particular types of seeds.

desirable for individual permanent seeds. In the last column of Table 1 is listed the activity required for permanent seeds implanted on a 1 cm. cubic lattice for the various volumes to deliver 7,000 r. Seeds of strength approximately 0.25 mc equivalent of radon (0.5 mm. Pt filtration) are probably the most useful.

CONCLUSIONS

The conclusions from the above analysis are as follows:

1. The dosage distribution in a seed volume utilizing a 1 cm. cubic lattice and uniform seeds is similar to the radiation distribution in a Paterson-Parker volume needle implant. There may be somewhat more variation in dose across the seed implant.

2. For an institution using the Paterson-Parker system, new tables are presented for the dose estimation in volumes 1 to 100 cm.^{3} implanted with equal seeds on a 1 cm. cubic lattice. Above 100 cm.^{3}, the Paterson-Parker tables are valid for this type of seed implant.

3. For 7,000 r in a permanent implant, seeds of strength about 0.25 mc equivalent of radon (0.5 mm. Pt equivalent filtration) are the most suitable for the seed volumes.

R. J. Shalek, Ph.D.
The University of Texas
M. D. Anderson Hospital
Houston 25, Texas

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DOSIMETRY OF MULTIPLE RADIATION FIELDS BY SUPERPOSITION OF PHOTOGRAPHIC FILMS*

By ROBERT LOEVINGER, PH.D., *and* JACOB SPIRA
NEW YORK, NEW YORK

IT IS well-known that photographic films can be used for dosimetry of supervoltage roentgen rays, and high-energy gamma rays. It is also well-known that, for direct action of roentgen and gamma radiation on the film, the density above fog is a linear function of exposure for exposures not too large.[1,2] As a result of this linearity of response and the additivity of photographic densities, a convenient method is available for studying the dosimetry of multiple, overlapping fields. If suitably exposed and developed films are superposed corresponding to the overlapping of the radiation fields, the resultant density is proportional to the total dose at each point, so the resultant dose distribution can be determined (in one plane) with a densitometer.

The superposition technique was developed for the study of a particular clinical problem. Carcinoma of the uterine cervix is treated at our institution with a tandem loaded with three radium capsules and a colpostat made of two ovoids each loaded with a radium capsule.[4] The olive-shaped ovoids are held by the colpostat at the maximum comfortable spacing in the lateral fornices, while (ideally) the uterine tandem is on the midline of the colpostat with one end tangent to the ovoids. In practice the tandem is often more or less skewed, or otherwise misplaced. The radiation therapy staff expressed a desire to investigate the dose distribution for a number of different spacings, alignments, and misalignments of these sources. Calculation of the complete dose distribution by the usual numerical methods would have involved a formidable amount of labor. Conventional methods of photographic dosimetry would have required making a phantom for each spacing to be investigated, and making a photographic exposure in each such phantom. Not only would such a program have been very time-consuming, but the radium sources would have been repeatedly handled in the darkroom. The task was greatly simplified by the superposition technique which is the subject of the present paper. Each radium source was used to expose a separate film. After development, the films were superposed corresponding to the spacing to be investigated. After the isodensity lines had been determined and recorded, the films were separated, adjusted to a new spacing, and the procedure repeated. A single set of original films was used to determine the entire series of dose distributions.

A typical film for a single source is shown in Figure 1. This film was exposed in a phantom, using the uterine tandem. The position of the source relative to the film—indicated by the lines on the edge of the film—was determined from the symmetry of the isodensity lines on the film after development, since it was not convenient to mark the position of the source relative to the film at the time of exposure. On the original film the isodensity lines could be traced with accuracy out to the edge of the film, though on the reproduction this would appear feasible only very near the source.

A typical superposition of three films (one tandem and two ovoid films) is shown in Figure 2. The films were assembled in the desired relationship on graph paper placed on an illuminated surface. Clear film or transparent plastic was placed on top, and the group was fastened together with a suitable tape. Using a photoelectric densitometer, points of a given density were marked, as shown in Figure 3. When these

* From the Andre Meyer Department of Physics, and the Department of Radiotherapy, The Mount Sinai Hospital, New York, New York.

FIG. 1. Single film exposed to 15–15–10 mg. of radium in the uterine tandem. The position of the sources is marked on the edge of the film.

points were connected with smooth lines, the final isodose curves were obtained. Figure 4 shows the complete isodose distribution determined from the group of films shown in Figure 2, superimposed on a cross-sectional diagram of the chief anatomic features of the female pelvis.

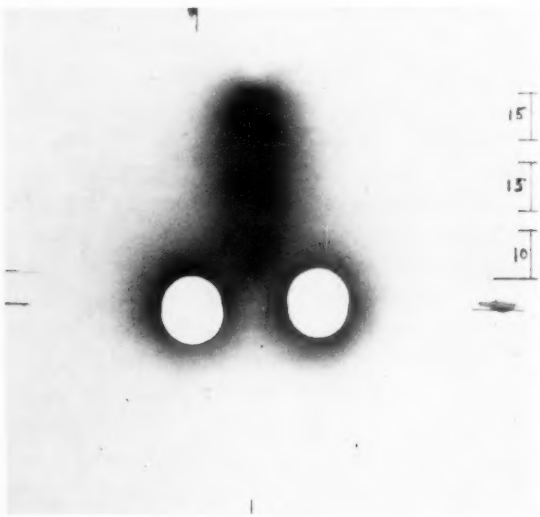

FIG. 2. Superposition of one tandem film and two ovoid films. The two white, oval areas are the holes cut in the ovoid films to receive the plastic ovoids.

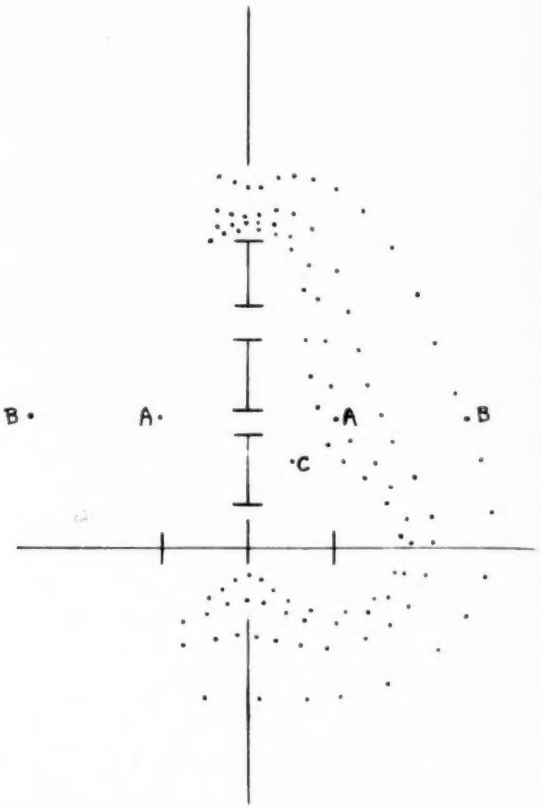

FIG. 3. Points of constant density, as recorded on a clear film covering the three films of Figure 2.

The basis of the assumption that the isodensity lines correspond to isodose lines can be explained as follows. The linear relationship between density and exposure for roentgen and gamma radiation[1,2] can be expressed in the following equation:

$$D = AE + B, \qquad D \leqq D_{\max}$$

where D is the measured density on a single film corresponding to the exposure E in roentgens or rad, B is the background fog density, slope A is a constant depending on processing conditions and related to the contrast (or gamma) of the film, and $D_{\max}$ is the largest density for which the linear relation is valid. Now photographic density is defined by the equation

$$D = \log I_0/I$$

where I_0 is the light incident on, and I the light emergent from the film. Then if two films are superimposed, the resultant den-

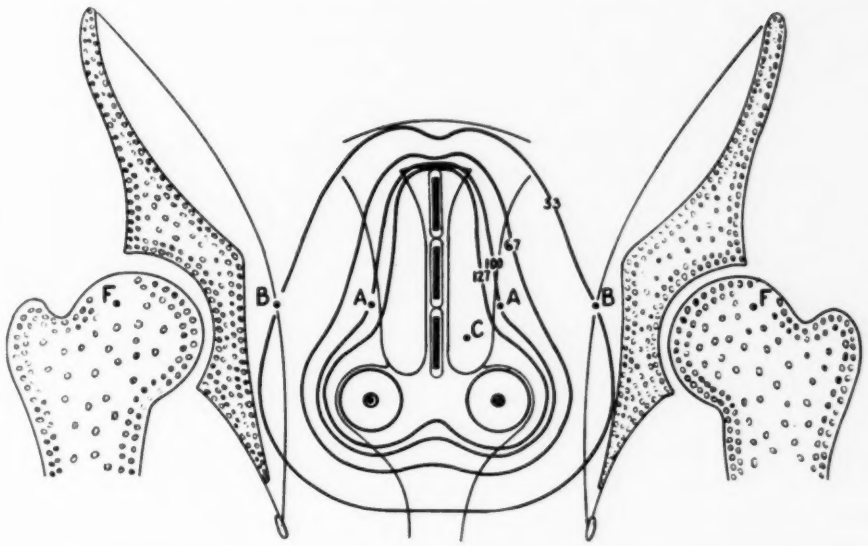

Fig. 4. Complete isodose distribution, determined from the films of Figure 2, superimposed on a cross-sectional diagram of the chief anatomic features of the female pelvis.

sity is the sum of the two original densities, for

$$D_1 + D_2 = \log \frac{I_0}{I_1} + \log \frac{I_1}{I_2} = \log \frac{I_0}{I_2} = D_{1+2}.$$

It follows that the resultant density also bears a linear relation to the sum of the exposures:

$$D_{1+2} = A(E_1 + E_2) + 2B.$$

This result can be extended to the superposition of any number of films. Thus, the measured density for several superposed films is a linear function of the sum of the individual exposures, provided each individual density falls within the linear part of the density-exposure curve.

The linearity of the density-exposure curve was tested by measuring the density on a single film exposed in a phantom, and computing the corresponding dose as a function of distance on the assumption that the "in phantom" dose is the same as the "in air" dose. While this is known to be accurate within about 10 per cent out to distances of 5 cm., recent results would allow a better computation of the dose as a function of distance.[3,5] The linear relation was found to hold up to a density of about 0.8 on the film used (see Table 1).

In a similar manner, the linearity of the resultant densities was verified for each assembled group of films. The dose to several specified points was computed by conventional means, and a density-dose graph was made for each group of films (as for example, the group shown in Figure 2), in each case verifying the consistency of the method.

The exposure time and conditions of processing and other technical details are

Table I

Summary of technical data for photographic superposition technique for multiple radium sources, as used to produce figures 1 to 4

Film: DuPont Adlux
Radium sources: 25 mg. in ovoids 1 cm. in diameter, and 15–15–10 mg. in the uterine tandem
Exposure: 200 minutes, in phantom of masonite pressdwood
Development: 12 minutes at 20°C. in 13 quarts of Du Pont 55-D, diluted 1 part stock solution to 12 parts water. Films agitated and permuted frequently during development
Fixing, washing, and drying: conventional
Background fog: $B = 0.08$ density unit, for unexposed and developed film
Slope of linear density-dose curve: $A = 0.35$ density unit per 100 roentgens
Upper limit to linear density-dose curve: $D_{max} = 0.8$ density unit.

shown in Table 1. They were chosen so that, for distances of clinical interest from the sources, the densities fell within the linear part of the density-exposure curve. Suitable holes were cut in the films to take the sources, the films were wrapped in black paper, and exposed separately to the individual sources in phantom. The films were all taken from one box, handled together, exposed simultaneously and for identical exposure times. The latter were sufficiently long to make negligible the times of assembly and disassembly of the phantoms. The films were developed together, thoroughly agitated, and systematically permuted in the developing tank to assure equal development. In order to improve the uniformity of development, the developer was diluted and the development time increased proportionately.

The film used for the procedures just described was chosen primarily for its slow speed. It has a translucent base, which results in the necessity for a small correction to the measured densities, due to the fact that the background densities do not add quite linearly. Film with a conventional transparent base shows strictly linear additivity, obeying accurately the above equations.

DISCUSSION

The dose distribution around multiple γ-ray sources can conveniently be studied by the present method provided the γ-ray energy is above about 0.5 mev.[2] A single set of films gives the dose distribution in one plane only. The relative position of the sources can, however, be adjusted as desired in planes parallel to the plane of the films.

A similar method can be applied to study of multiple field dosimetry in radiation therapy with Co^{60}, Cs^{137}, and all roentgen ray machines with energies above 1 mev. peak.

Photographic dosimetry fails for roentgen ray energies much below 1 mev. peak, due to the high sensitivity of the film to the low-energy scattered radiation.[2] Since the use of multiple field techniques is more important with conventional voltage therapy than it is with supervoltage therapy, it is unfortunate that the present photographic superposition method is not directly applicable. The additivity of densities could, however, be utilized if dose distributions determined by ionization methods were converted to continuous density variations on a film. With a set of such films for (say) 200 kv. peak roentgen ray fields, planning of multiple field radiation therapy would be greatly simplified.

Robert Loevinger, Ph.D.
Physics Department
1 E. 100th Street
New York 29, New York

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THE INFLUENCE OF TREATMENT CONES ON DOSE RATE

By NORMAN A. BAILY, Ph.D., *and* NORMAN S. BEYER, M.A.
Department of Radiation Therapy, Roswell Park Memorial Institute
BUFFALO, NEW YORK

THE fact that cones and diaphragms influence dosage rate as measured in air is well known to radiologic physicists. However, the extent to which such factors need to be taken into account is not extensively treated in the radiologic literature. Epstein, *et al.*[3] have published figures showing that the diaphragm and side wall influence the intensity of radiation found at the cone face.

These two factors tend to produce opposite effects on the dose at the cone face. The diaphragm because of the finite focal spot area will reduce the radiation emerging from the cone. The walls of the cone on the other hand, will tend to increase the amount of radiation at the face due to scattering from the walls. As will be shown, under our experimental conditions this added radiation is extremely soft when compared to the quality of the primary beam. This has been pointed out previously by Quimby and Marinelli.[4] The contributions to the depth and surface doses from such scattered radiation must be carefully considered. Not only is it lower in quality than the radiation in the primary beam, but as shown by Eddy and Stevens,[2] it traverses the face of the cone at such an angle that it is all outside of the geometric beam limits 3 cm. below the face of the cone. However, this observation was made in air and particularly in the case of small fields, such radiation may be scattered back into the beam when tissue intervenes.

The primary objective of this experiment was to provide quantitative information on standard treatment cones used routinely by both radiologists and dermatologists. In addition, some measurements on the influence of the diaphragm alone have been made. These measurements show that in the case of the smallest cones where a decrease in dose rate was found, the decrease was of the same order of magnitude as that found using only the diaphragm. However, in the case of the larger cones, no part of the measured increase in dose rate was due to the diaphragm.

EXPERIMENTAL MEASUREMENTS

Measurements were made at peak potentials of 70, 100, 140, 200 and 250 kv. This energy range encompassed half-value layers ranging between 0.25 mm. Al and 2.1 mm. Cu.

Dose rates were measured in free air with diaphragms and with cones always keeping the ionization chamber in one position so that the results to be given below would be independent of any scattering from walls or supporting structures. Care was taken to reduce the contribution of such scattering to a minimum. This position was so chosen that the geometric center of the ionization chamber was at the center of the cone face. Ionization chambers used were calibrated against a standard air chamber. Correction was also applied for non-linearity of the "r" meter scale at high scale readings. Corrections for absorption in the chamber walls for low energy radiation was made using the data of Day.[1] A Victoreen 250 r nylon wall chamber was used for all measurements. This chamber has a wall thickness of 0.005 inches. Its active volume is 6 mm. in length.

All cones used were open face and of the shape used for superficial therapy and for intracavitary applications of deep therapy equipment. These cones were of the following types. Those used for measurements made in the range of 70 to 100 kv. peak in conjunction with a beryllium window tube are shown in Figure 1. The dimensions of

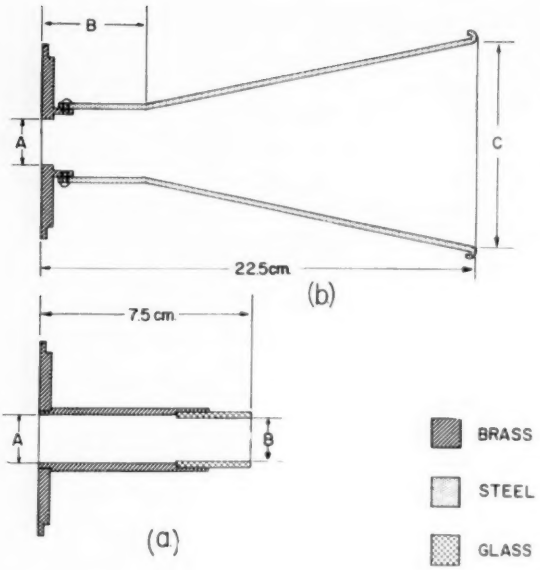

FIG. 1. Treatment cones for use with General Electric Maximar 100. These cones were used to obtain data for 70 and 100 kv. peak radiations generated by a beryllium window tube.

these cones are given in Table 1. Cone types used at 100, 140, 200 and 250 kv. peak with conventional tubes are shown in Figure 2. These are shown schematically and are not working drawings of these cones. Cones shown in Figure 2*b* when used with 200 kv. peak were lined with 1 mm. of lead. In all cases, the combination diaphragm and clamping plate were equipped either with sufficient thickness of brass or lead to reduce radiation outside the area defined by the cone to 1 per cent or less of the useful beam. The cones shown in Figure 2*b* in some cases were used in conjunction with a visual localizer type adapter. The effect of such attachments will be discussed below. The pertinent dimensions and geometric considerations for these cones are given in Table II.

When studying the effects of the visual localizer adapters, the ionization chamber was kept at the same distance as had been used for recording the values using the cones in conjunction with these adapters. For some cones, the openings in these adapters served, partially at least, as the limiting diaphragm. Such units were used

TABLE I

DIMENSIONS OF TREATMENT CONES SHOWN IN FIGURE 1. THESE CONES WERE USED TO OBTAIN DATA ON THE INFLUENCE OF SUCH CONES FOR 70 AND 100 KV. PEAK ROENTGEN RAYS

(*a*) F.S.D.—15 cm.

A (cm.)	B (cm.)	Area of Cone (cm.²)
0.95	0.96	0.763
1.73	1.49	1.77
2.07	2.03	3.21
3.00	2.68	5.56
4.32	3.96	12.4
4.76	4.74	18.1

(*b*) F.S.D.—30 cm.

A (cm.)	B (cm.)	C (cm.)	Area (cm.²)
1.41	7.33	5.08	20.3
2.85	4.00	10.2	82.2
4.37	3.00	15.2	181
5.78	2.72	20.2	320

in conjunction with measurements made at 100 and 140 kv. peak, focal skin distance, 37 cm. and at 250 kv. peak, focal skin distance, 46 cm. The diaphragm diameter

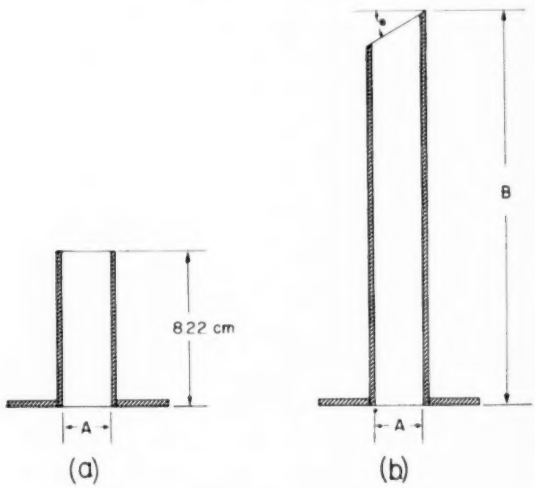

FIG. 2. Treatment cones for use on 100, 140, 200 and 250 kv. peak roentgen therapy units. These cones were used to obtain data on the influence of such cones on dose rate and beam quality at these energies.

TABLE II

DIMENSIONS OF TREATMENT CONES SHOWN IN FIGURE 2. THESE CONES WERE USED TO STUDY THEIR INFLUENCE ON DOSE RATE USING 100, 140, 200 AND 250 KV. PEAK ROENTGEN RAYS

Figure 2*a*

100 and 140 kv. peak—F.S.D. = 18 cm.	
A (cm.)	Area (cm.²)
1.57	1.94
2.32	4.22
3.50	9.62
4.82	18.2

Figure 2*b*

100 and 140 kv. peak—F.S.D. = 37 cm.		200 kv. peak—F.S.D. = 38 cm.		250 kv. peak—F.S.D. = 46 cm.	
B = 18 cm.; $\theta = 28.8°$		B = 14.2 cm.; $\theta = 36.2°$		B = 18 cm.; $\theta = 28.8°$	
A (cm.)	Area (cm.²)	A (cm.)	Area (cm.²)	A (cm.)	Area (cm.²)
3.00	7.07	2.02	3.20	3.00	7.07
3.47	9.45	2.51	4.95	3.47	9.45
4.01	12.6	2.98	6.97	4.01	12.6
5.06	20.1	3.44	9.29	5.06	20.1

was 4.75 cm. while the diameter of the largest cone was 5.07 cm. In the unit used at 200 kv. peak the lead diaphragm associated with the localizer was only 3.18 cm. in diameter and the diameter of the largest cone used was 3.48 cm. We should like to point out that these are standard units and cones that are now in rather wide use.

In addition to ionization measurements, roentgenograms were taken for each cone used and at each energy where the particular cone was used. These films were examined for gross irregularities in field distribution and then measured with a densitometer. Density measurements were made across the field at 1 cm. intervals in two lines at 90° to each other.

Although the dimensions of the ionization chamber used are quite small, the feasibility of using the above technique in conjunction with small cones might be questioned. Two experiments were performed to investigate the possible error that might be introduced. The first experiment consisted of placing the chamber perpendicularly to the beam as closely to the cone edge as possible. The chamber was then moved away from the cone a distance equal to the original distance between the cone face and the center of the chamber. The difference between the two readings was then added to the first to obtain the value at the cone face. This value was 0.6 of 1 per cent lower than that obtained by the method described above. The second experiment was designed to check the dependency of the chamber reading on position of the chamber in the beam. Readings were taken with the chamber center always in one position while the stem was rotated from an initial position parallel to the beam and along its central axis to a position making an angle of 45° to the beam. The experimentally determined values show a dependency of less than 1 per cent for all positions making an angle of 10° or more with the beam.

Studies to determine the influence on quality of cones used in conjunction with both low and high voltage roentgen rays were made. These included the determination of the half-value layer of these beams both with and without cones present. The influence of cone size on this quantity was also studied. Absorption curves were run for all cases of interest so that changes in the soft component might be detected. The absorbers used were placed directly across the cone face. The chamber was then placed sufficiently far from the absorbers so that no contribution from secondaries generated in these would be recorded.

RESULTS

Quantitative Effects. The experimentally determined ratios of dose rate with cone to that as measured in free air for the cones shown in Figure 1*a* are given in Figure 3. The curves shown here were obtained using a General Electric Maximar 100 having a

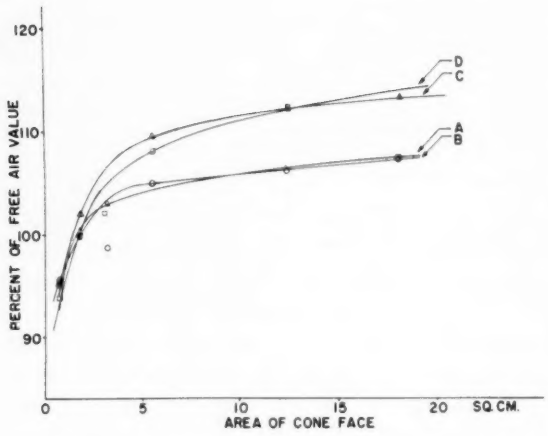

FIG. 3. Experimentally determined ratios of dose rate with cones shown in Figure 1*a* to that found in free air. These ratios were determined when these cones were used in conjunction with a beryllium window roentgen tube operating under the following conditions: *Focal Skin Distance—15 cm.* Curve A—70 kv. peak; 0.25 mm. Al filter. Curve B—100 kv. peak; 0.25 mm. Al filter. Curve C—100 kv. peak; 1.0 mm. Al filter. Curve D—100 kv. peak; 3.0 mm. Al filter.

beryllium window tube. Curve A was obtained for 70 kv. peak operation using a 0.25 mm. aluminum filter. Curves B, C and D were measured with an operating potential of 100 kv. peak and filters of 0.25 mm., 1 mm., and 3 mm. of aluminum, respectively. The approximate half-value layers for these radiations are: 0.25 mm. Al, 0.4 mm. Al, 1.4 mm. Al and 3.1 mm. Al, respectively.

These results show first, that there is a tendency for very small cones and their associated small diaphragms to restrict the beam so that a loss of intensity is encountered. As the area of the cone is increased, a rapid increase of beam intensity with area is found. This is then followed by a more gradual increase with increasing area. This more gradual increase seems to be very nearly constant for areas over 5 cm.^{2} and the two softest radiations. In the case of the two harder radiations, this occurs for areas exceeding 10 cm.^{2}. It should also be noted that the radiation intensities fall into two distinct groups differing by approximately 6 per cent. The differences between the curves A, B and C, D are not significant and approach the experimental accuracy.

Utilizing the same qualities of radiation, the influence of larger cones such as illustrated in Figure 1*b* was studied. The results for these cones are shown in Figure 4. It is interesting to note that even for large area cones of this particular geometry, scattering from the walls of the cone is not enough or may just compensate for the cut-off of the beam by the diaphragming. Only with the hardest radiation used (half-value layer 3.1 mm. Al) does the dose rate become larger than that found in free air and then only by some 2.7 per cent.

In view of the results obtained above, the cones shown in Figure 2*a* which are used for intra-oral and intracavitary therapy at higher energies were investigated. The results for these cones are shown by the curves in Figure 5. Curve A shows the ratio of dose rate with the cone to that in free air when these cones were used with a tube having a glass window operated at 100 kv. peak without additional filtration. The half-value layer for this radiation is 1.5 mm. Al. Curve B shows the results for

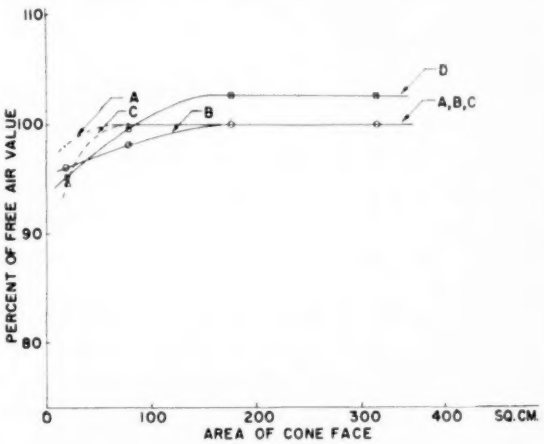

FIG. 4. Experimentally determined ratios of dose rate with cones shown in Figure 1*b* to that found in free air. Operating conditions: *Focal Skin Distance—30 cm.* Curve A—70 kv. peak; 0.25 mm. Al filter. Curve B—100 kv. peak; 0.25 mm. Al filter. Curve C—100 kv. peak; 1.0 mm. Al filter. Curve D—100 kv. peak; 3.0 mm. Al filter.

this same tube using the same cones but operated at 140 kv. peak and filtered by 0.25 mm. Cu plus 1 mm. Al. The half-value layer of this radiation is 0.44 mm. Cu. It is interesting to note that the scattering from the cone walls in this case is significantly higher for the lower quality radiation, although the behavior of the scattered contribution apparently follows similar patterns for both qualities. The difference in the scattered contribution remains essentially constant over the range of cone sizes used (4 per cent for an area of 1.94 cm.^{2} and 5 per cent for an area of 18.2 cm.^{2}).

Intracavitary cones such as shown in Figure 2*b* are often used for deep therapy. Therefore, data were obtained using these cones in conjunction with roentgen-ray beams having peak energies of 200 and 250 kv. peak. The qualities of these radiations were half-value layer 0.9 mm. Cu and 2.1 mm. Cu. In addition, they were used with radiations previously discussed having half-value layers of 1.5 mm. Al and 0.44 mm. Cu. This was done to allow a comparison under the same geometric conditions and at approximately equal focal skin distances for a large range of qualities. The conditions under which the results shown in Figure 6 were obtained are summarized in Table III. Curve A was determined using radiation generated at 100 kv. peak and having a half-value layer of 1.5 mm. Al. Curve B at 140 kv. peak, half-value layer of 0.44 mm. Cu. Curve C was obtained using 200 kv. peak and a half-value layer of 0.9 mm. Cu, while the experimental points for D were determined at 250 kv. peak and at a half-value layer of 2.1 mm. Cu.

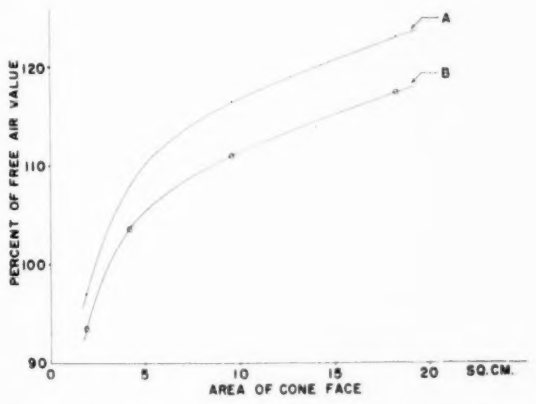

FIG. 5. Percentage of free air dose for cones shown in Figure 2*a*. These cones were used in conjunction with a roentgen ray beam generated at the indicated potentials by a conventional tube under the following conditions: *Focal Skin Distance—18 cm.* Curve A—100 kv. peak; no filter. Curve B—140 kv. peak; 0.25 mm. Cu + 1.0 mm. Al filter.

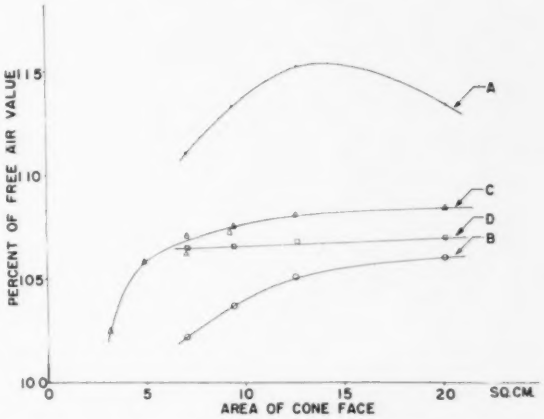

FIG. 6. Percentage of free air dose obtained using the intracavitary cones shown in Figure 2*b*. Other pertinent data for these curves are given in Table III. Curve A—focal skin distance, 37 cm.; half-value layer, 1.5 mm. Al. Curve B—focal skin distance, 37 cm.; half-value layer, 0.44 mm. Cu. Curve C—focal skin distance, 38 cm.; half-value layer, 0.9 mm. Cu. Curve D—focal skin distance, 46.5 cm.; half-value layer, 2.1 mm. Cu.

Here, as predicted by theory, the scattering from the walls of the cones decreased with the increased energy of the beam. This is demonstrated in the differences between curve A and those measured with higher energy beams. The differences between the values obtained at 140 kv. peak and those at 200 and 250 kv. peak are small except for the smallest cones used. Another interesting feature demonstrated by the 100 kv. peak curve is the drop in dose rate for the 20.1 cm.^{2} cone. Such a fall-off is not yet in evidence at the higher energies.

It is of interest to know what portion of the radiation found at the cone face has been affected by various cone adapters, especially those containing a light localizer.

TABLE III

EXPERIMENTAL CONDITIONS USED TO OBTAIN DATA ON THE CONTRIBUTION OF INTRACAVITARY CONES TO DOSE RATE AS MEASURED IN AIR

Kv. Peak	Filter	F.S.D.	H.V.L.
100	0	37 cm.	1.5 mm. Al
140	0.25 mm. Cu+1 mm. Al	37 cm.	0.44 mm. Cu
200	0.5 mm. Cu	38 cm.	0.9 mm. Cu
250	0.23 mm. Sn+0.25 mm Cu+1 mm. Al	46.5 cm.	2.1 mm. Cu

It was found that these affected the free air dose rate in all cases by less than 1 per cent, the average value being 0.4 per cent.

Another factor of interest to the therapist using such cones is the variation of intensity in various portions of the beam. Since the areas of these beams are small, measurements with ionization chambers are not practicable. We have, therefore, used photographic techniques for this work. Measurements of the film densities were made using an Ansco densitometer having a light beam width of 3 mm. Densities were determined every 5 mm.

The intensity distribution as determined photographically showed surprising uniformity. Except at the very edges, the densitometer readings remained constant within the limits of the instrument. The maximum deviation recorded was 2 per cent. At the edges, the fall-off was as great as 10 per cent. However, this band of lower intensity did not extend in any case more than a few millimeters.

Qualitative Effects. In addition to a knowledge of the quantitative effects produced by small cones on the dose rate, it is important to know specifically the changes which occur in the quality of the beam. To determine whether such changes actually do exist and to see the magnitude of such changes, absorption curves were run at the lowest and again at the highest energies used previously.

Absorbers were placed in contact with the cone face wherever possible, and in the case of the slant face cones the absorbers were placed at right angles to the axis of the cone and in contact with the longer edge. The ionization chamber was placed so that secondaries and radiation scattered by the absorbers were not contributing to the recorded dose rate. In some cases, several size cones were used to obtain data which might help to establish the quality of the radiation causing the observed increase in beam intensity.

Measurements made at 70 kv. peak using a beryllium window tube and additional filtration of 0.25 mm. of aluminum are shown in Figure 7. These measurements were obtained using cones having areas of 0.74 and 12.38 square centimeters (curves B and C, respectively). Also shown for comparison is the absorption curve obtained when no cone is used to collimate the beam (curve A). Although the actual differences in half-value layer of these radiations is small (6.5 per cent) the free air curve shows the highest quality, as would be expected. However, the beam emanating from the larger cone has a slightly higher half-value layer (2 per cent) than that coming from the small cone. When less than 0.23 mm. of aluminum is in the path of the beam, this relationship between cones is reversed. However, due to the fact that the experimental data had to be corrected for wall absorption, we feel that the precision of the corrected values is not sufficiently high to state that this is a real effect. This impression is substantiated by the fact that if one plots the uncorrected data, no such reversal is found. Also, as will be seen, no reversal is found for higher energy beams. Therefore, it is probably better to take the differences at 0.1 mm. aluminum as an indication of the quality differences. The

differences here are approximately 3 per cent between each value.

For radiation generated by the same tube at 100 kv. peak and filtered by 1 mm. of aluminum, the relationship is similar to that of the lower energy radiations shown in Figure 7. As can be seen by the absorption curves in Figure 8, no reversal occurs. Here the half-value layer for the large area cone is 13 per cent lower than that for the free air determination and 5 per cent lower than that of the beam emerging from the small area cone. After the addition of 0.5 mm. of aluminum, the relationship between these curves is constant, indicating that the soft component added by the cones is removed by this thickness of aluminum.

Similar curves were determined for the hardest radiation used. This was a 250 kv. peak beam filtered by a composite filter of 0.23 mm. Sn, 0.25 mm. Cu, and 1 mm. Al. Within the limits of experimental error, no differences in the half-value layer as measured in free air and that measured with cones in place was perceivable.

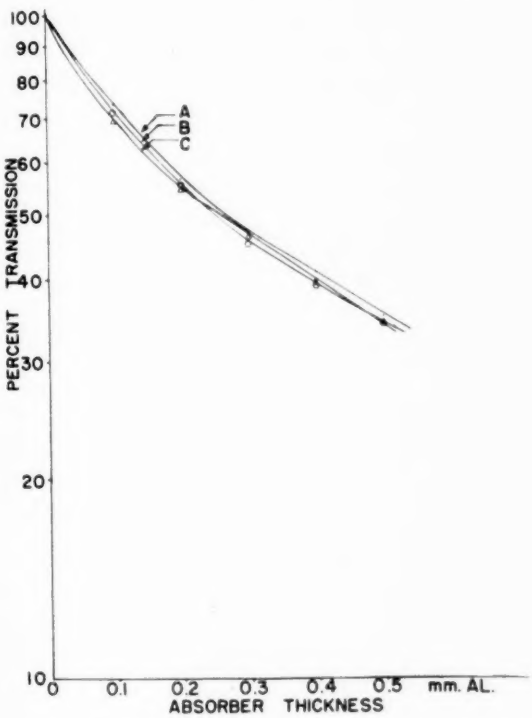

Fig. 7. Absorption in aluminum of a radiation beam generated at 70 kv. peak by a beryllium window tube, filtered by 0.25 mm. of aluminum. Curve A—free air. Curve B—cone face area = 0.74 cm.². Curve C—cone face area = 12.38 cm.².

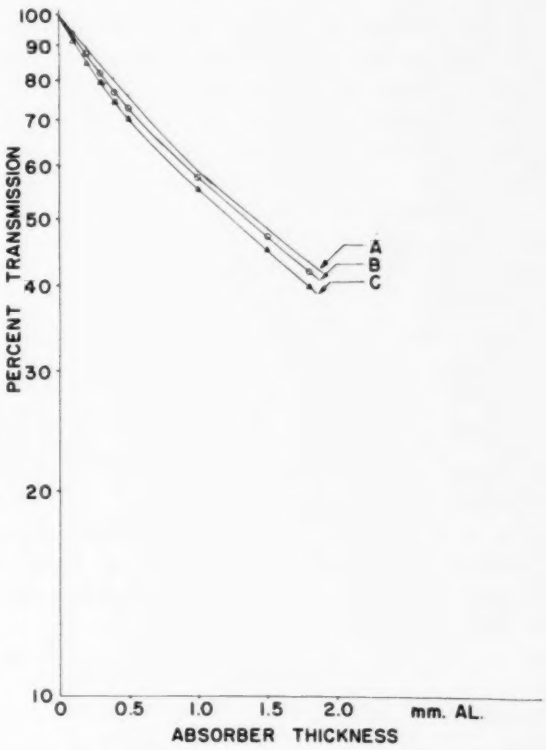

Fig. 8. Absorption in aluminum of a radiation beam generated at 100 kv. peak by a beryllium window tube with additional filtration of 1.0 mm. of aluminum. Curve A—free air. Curve B—cone face area = 0.74 cm.². Curve C—cone face area = 12.38 cm.².

DISCUSSION

The use of small cones such as used in superficial or intracavitary roentgen therapy requires special calibration with the cone of interest in place. The extent to which such cones will modify the dose rate incident on the skin depends upon several factors. These factors are: the area of the diaphragm opening, area of the cone face, the geometic configuration of the cone, cone length and the quality of the radiation beam.

Changes in the dose rate in many cases are great enough to be of practical importance. Such changes affect the ratio of skin

to tumor dose differentially, since the ratio is both energy dependent and a function of the geometric factors involved. It is therefore necessary for the therapist to be aware of such changes and the extent to which these affect his particular treatment techniques.

SUMMARY

The effects on beam intensity and quality of a variety of treatment cones such as are used in superficial therapy and for intraoral and intracavitary therapy with high voltage roentgen rays have been studied. Changes in dose rate have been found to range between negligible amounts and 23 per cent with the curves indicating that even larger deviations are possible. Changes in quality have also been found, the absorption curves showing an increased soft component in the beam when cones are present.

Norman A. Baily, Ph.D.
Department of Radiation Therapy
Roswell Park Memorial Institute
Buffalo 3, New York

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THE TRANSITION EFFECT AT LOW ROENTGEN-RAY ENERGIES*

By W. S. MOOS, Ph.D.

CHICAGO, ILLINOIS

THE amount of radiation energy absorbed in a biologic object is dependent on several factors. To name just some of the most important ones, we have to consider the absorption characteristics of the material, linear energy transfer, and the transition effect. All these factors are variable with changing energy of the primary beam of radiation.

In the case of irradiation with directly ionizing particles of uniform velocity, the calculation of absorbed energy (erg/gram) within a specified volume of tissue is somewhat less complicated than if one deals with indirectly ionizing radiation, such as roentgen or gamma rays.

Many attempts have been made to calculate or measure the total roentgen-ray energy absorbed. Most of these thoughts and experiments are directed toward the application in human therapy or tests in larger animals.[1,2,3,12,13] However, not until recently has the need for consideration of similar factors in microbiologic radiation work been emphasized. Especially important for radiation experiments with very small objects, such as bacteria, virus, phage, is the evaluation of the transition effect on the samples.[4,14]

In this paper it will be our main concern to provide data on the variation of dose received by such a small object exposed to roentgen radiation in which electronic equilibrium is attained at different levels of absorption depth.

For the sake of explanation a simplified model drawing of the transition effect is shown in Figure 1.[10] The absorber is considered to be formed of sections of constant thickness. The number of secondary electrons produced per cm.^{2} should be equal in each of these sections, neglecting attenuation of the roentgen-ray beam. Provided that we assume a constant electron range we can say that the ionization intensity in all sections is approximately proportional to the number of electrons passing through it. The upper theoretically deducted curve (a) shows that the intensity will reach a level where it remains constant. This level starts at a depth which corresponds very closely to the range of the electrons of one particular energy. As mentioned before, this is a simplification of the actual phenomenon. In reality one has to consider roentgen-ray intensity diminution caused by the inverse square correction and by energy transfer to Compton electrons and particles created in the process of pair production taking place in successive layers of absorber, curve (b).

Trump[16] as well as Harvey, *et al.*,[6] Johns and co-workers,[9] and Laughlin,[11] observed transition effects while studying the depth dose distribution of roentgen rays obtained by multimillion electron volt generators

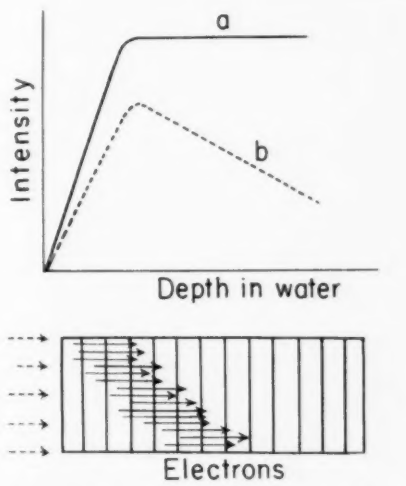

Fig. 1

* From the Department of Radiology, College of Medicine, University of Illinois, Chicago, Illinois.

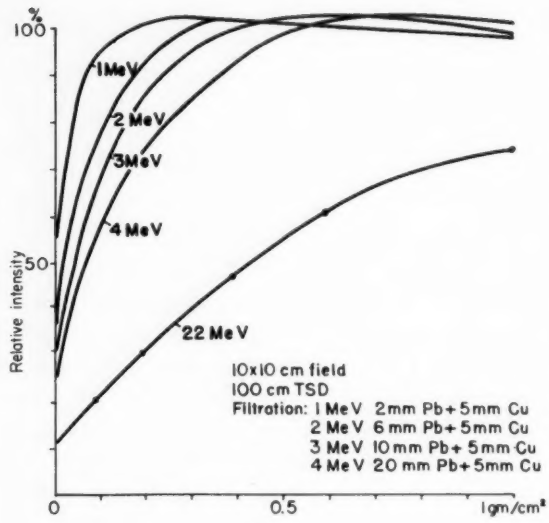

FIG. 2

such as Van de Graaff apparatus, Betatron, etc. Figure 2 demonstrates such an effect obtained with 22, 4, 3, 2, and 1 mev. roentgen rays. This set of curves shows that the equilibrium of transition is reached (100 per cent intensity) at an absorber depth which is approximately equivalent to the mean range of the secondary electrons in water. For 22 mev. roentgen rays this is about 4 cm. and for 2 mev. roentgen rays 3 to 4 mm.

It is easily understandable from this discussion and drawings that consideration of the transition effect becomes of as great importance in the dosimetry of roentgen or γ-ray irradiated small biologic objects as it is in the roentgen therapy of malignant disease. Very small objects such as cells would obtain only a fraction of the maximum dose while irradiated with high energy roentgen rays unless tissue or cell equivalent material is placed in front of them to provide build up to electronic equilibrium at the location of the object.

To our knowledge no extensive study of

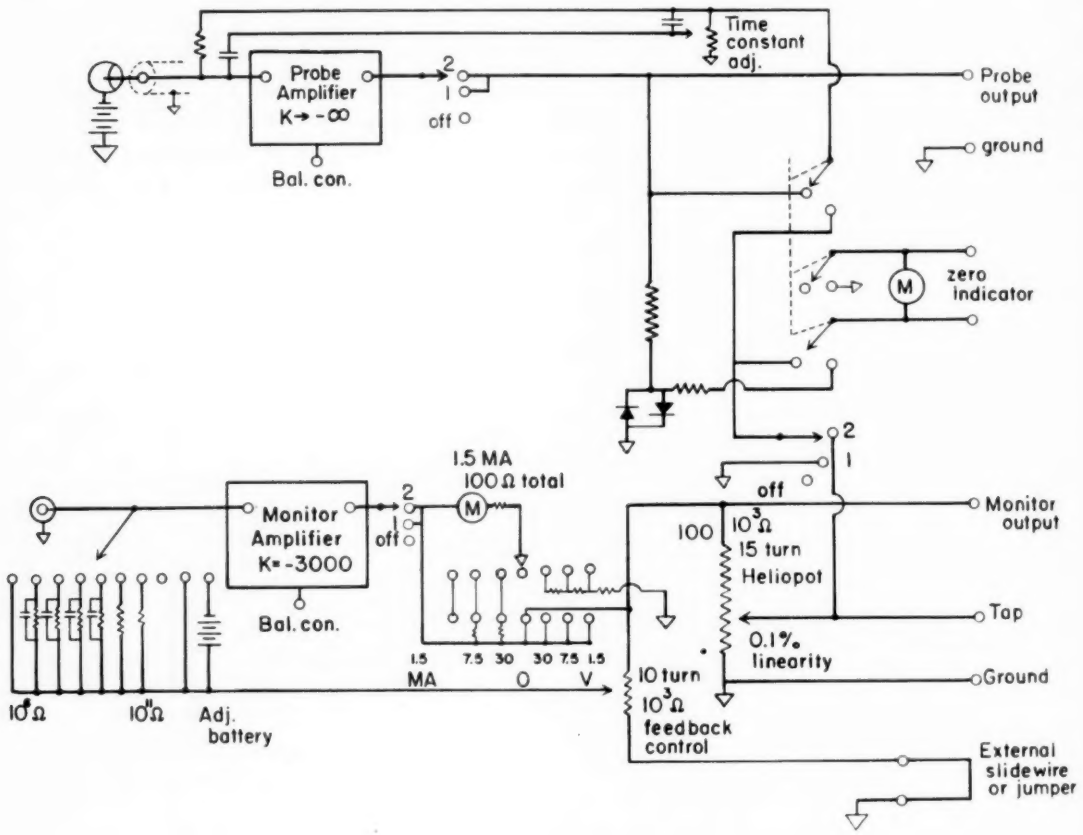

FIG. 3

the transition phenomena has been performed below the 400 kv. peak roentgen-ray energy level, though many microbiologic radiation experiments are carried out at roentgen-ray energies far below the energies where data of this nature would be available. For this reason the transition effect has been determined by us for radiation energies as low as 50 kv. peak roentgen rays.

EXPERIMENTAL APPARATUS

The equipment employed in our experiments consisted of three units: a monitor ionization chamber, a remote controlled extrapolation ionization chamber and a two channel DC amplifier (Fig. 3). Each channel was a feedback type current amplifier with electrometer tubes in the input stages. The outputs of the two channels were compared with each other over a 15 turn 0.1 per cent linearity potentiometer using a nil reading galvanometer. To eliminate cable noise in the extrapolation chamber channel, the electrometer tube and a 10^{11} ohm resistor were mounted in a small probe and connected directly to the chamber. This arrangement was selected to prevent intensity variations of the roentgen-ray output to interfere with the measurements. The simple construction of the monitor chamber does not need further discussion.

The extrapolation chamber was built from a cylindrical piece of lucite in which a spring-loaded piston (1.4 cm. ϕ) of the same material moved up and down. This up and down movement was caused by a selsyn-activated micrometer screw. The head part of the piston carried the collection (0.6 cm. ϕ) and guard ring electrode assembly. The fixed top electrode was formed by a 6 μ thick Mylar film. The window or top electrode as well as the piston electrode was produced by a thin layer of Aquadac. The chamber always worked under saturation conditions, even at maximum electrode spacing when a collection voltage of over 12 to 14 volts was applied. The beam defining mechanism

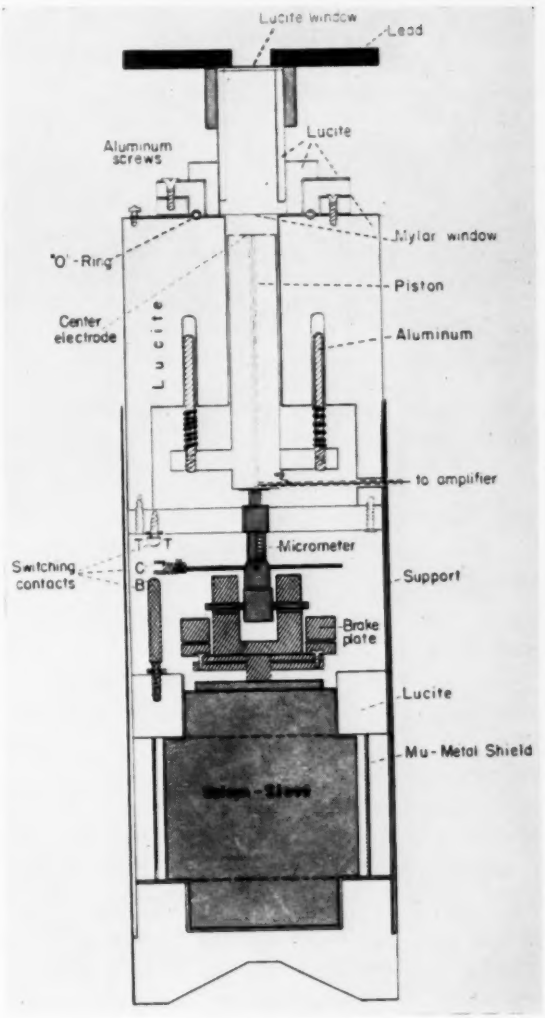

FIG. 4

consisted of a 10 cm. long lucite extension tube topped by a lead-lucite diaphragm combination. This part of the chamber could be removed to allow the placing of absorber foils on top of the Mylar electrode but insuring at the same time the reproducibility of geometry while replacing it. A more detailed description of this chamber is published elsewhere.[15] A cut view of the extrapolation chamber is reproduced in Figure 4.

RESULTS AND DISCUSSION

Measurements in the low roentgen-ray energy range were made with a Keleket Thermax unit using a Machlett beryllium

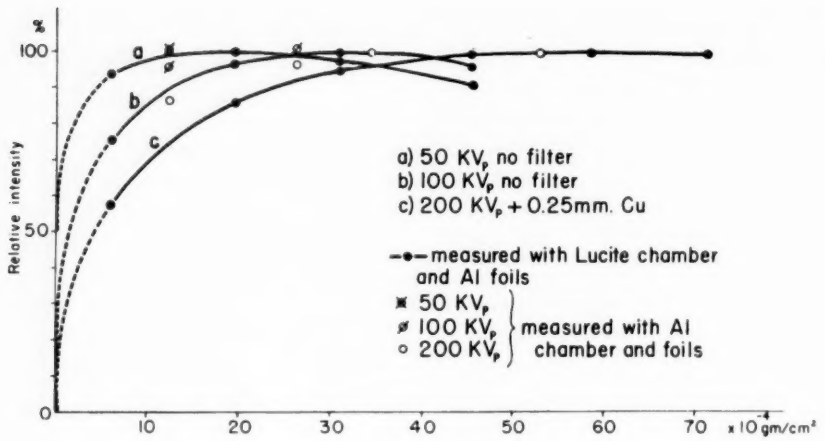

FIG. 5

window tube with 0.6 mm. Al inherent filtration. The distance from target to the top electrode of the extrapolation chamber was 40 cm.

The ionization current in both chambers was amplified in the two channels of the amplifier and the instrument was balanced for zero indication with no absorber foils in the extrapolation chamber except for the Mylar electrode. The ion currents in the monitor chamber and extrapolation chamber were in the order of magnitude of 10^{-8} and 10^{-11} amperes, respectively. After these adjustments were completed, foils of 5 μ thick pure aluminum (2 cm. ϕ) were placed on top of the Mylar electrode of the extrapolation chamber and the roentgen-ray yield switched on again.* The increase of ion current due to the Al-foils in the small volume of the chamber was determined at different electrode separations and the slopes of the curves obtained in this manner were compared with the tangent of the curve produced without absorbers. These extrapolation curves proved to be linear up to plate separations of about 0.1 cm.

The relative increase of ionization with increase of absorber thickness is plotted in Figure 5 for 50, 100 and 200 kv. peak. The thickness of the absorbers is given in gm./cm.^{2} It is obvious from this set of curves that roentgen rays of as low an energy as 50 kv. peak are able to produce some transition effect which may be of significant magnitude for microbiologic investigations.

It was realized that the use of aluminum foils will have some effect on the otherwise tissue equivalent material of the chamber.[5,7,8] For this reason a second experiment was carried out. The measurements were repeated as described above with an extrapolation chamber built entirely from aluminum, but which was otherwise identical in construction with the lucite chamber.**

CONCLUSION

The transition effect in roentgen irradiated objects has been observed at very high energies. Since many microbiologic investigations of roentgen-ray effects are carried out at lower roentgen-ray energies it has been the question to what a degree such transition phenomena will influence the obtained data. It has been found that such an effect may be of significant magnitude at roentgen-ray energies as low as 50 kv. peak.

The thickness of the absorber is of importance. Furthermore, it is preferable to

* Al-foils were employed instead of tissue equivalent Mylar since the latter produced technical difficulties in stacking a sufficient number of layers on top of each other, due to electrostatic charges.

** The values obtained with this type of chamber are also indicated in Figure 5.

place the biologic objects always in an area where maximum build up has been achieved. Once this maximum is reached only small variations occur over a considerable thickness of absorber compared to the very thickness of the object to be irradiated itself.

Department of Radiology
University of Illinois
840 South Wood Street
Chicago, Illinois

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AN APPRAISAL OF THE STATISTICAL REPORTS ON THE RESULTS OF THERAPY*

By HAROLD TIVEY, M.D., *and* VINCENT P. COLLINS, M.D.
HOUSTON, TEXAS

STATISTICAL analysis represents only a formalized method of thinking. Statistical processes, like any other form of logic, can be misused in the same way that the classic cartoonist's drunk uses a lamp post—more for support than illumination. The primary function of the statistical methods is to illuminate the results of therapy and to supplement, to confirm or to modify clinical impressions. This brief discussion is limited to the problem of analysis of the results of treatment already given. Statistical methods can be extremely valuable in the formulation of plans for clinical research, but this is a separate problem. No unpublished methods are proposed, some new and relatively unused methods will be briefly reviewed, and some existing problems pointed out, in the the hope that a joint effort will provide a speedier solution.

THE PATIENTS AND WHAT WAS DONE TO THEM

"If the rules are relaxed in any way, it is remarkable how results may be improved by whittling away unsuitable cases."—McWhirter.

Every reported series is published with the implied or expressed purpose of comparison with the results of others. If the patients reported are quite different from those seen in your own practice, the methods used and the results achieved may not be applicable to your problems. The conditions of private medical practice make some selection unavoidable in most American series. It would appear an important responsibility of each author to define as carefully as possible all of the factors which may have led the patient to select his method of treatment, to describe the state of the patient's disease, and to outline completely the method of treatment, including all adjuvants which may be effective in prolonging life.†

Treatment policies affect the selection of patients for treatment, since referring physicians may understandably fail to refer a patient for operation if the patient is in a published "categorically inoperable" group. Such selection avoids unnecessary procedures and is of benefit to the patient and to the physician. Careful selection of cases will lead to better results on those treated, but it is easy to attribute this improvement to the treatment rather than to the selection. As an example, cure rates in carcinoma of the breast constantly improve in the published series, but the total mortality from this disease shows little change.[5] Increasing selection can lead to results that approach perfection on a limited number of patients, scarcely a satisfactory answer to the problem of the majority of patients.

FACTORS WHICH MAY BE CONSIDERED IN THE EVALUATION OF TREATMENT

The problem of satisfactory measurement of the result for the individual is not a simple one. On a clinical basis, we are inclined to rely on experience with other patients. An asymptomatic patient, living at a time when he should have died of his disease if untreated, is taken as satisfactory evidence of the effectiveness of treatment. In the past, this empirical approach

† A pertinent example is the use of androgens in the treatment of metastatic carcinoma of the breast. The published work of Hallberg, Nohrman and Sylven[6] would indicate that this may prolong life typically more than six additional months in the postmenopausal female. More obviously, a colostomy can prolong life in carcinoma of the rectum by preventing obstruction but has no effect on the tumor.

* From the Department of Radiology, Baylor University College of Medicine, Houston, Texas. Presented at the Thirty-eighth Annual Meeting of the American Radium Society, Houston, Texas, April 9–11, 1956. This work is supported in part by research grant U.S.P.H. C-2715 from the National Institutes of Health, United States Public Health Service.

has been sometimes compatible with the capabilities of our equipment.

With the medium voltage therapy machine, the maximum amount of radiation to a deep seated tumor was determined by the relative sensitivity of the patient's skin and the ingenuity of the therapist. With supervoltage equipment, the skin is no longer a barrier to massive therapeutic doses. The removal of this barrier now makes possible further investigation directed toward finding the true range of depth doses required to destroy a given tumor in a given location.

"Early" lesions now treated surgically might be treated more simply with less inconvenience to the patient, using supervoltage techniques. Before this change can be made, the referring physician may reasonably ask—"Can you deliver a cancerocidal dose?" The answer to this question need not come from such early cases alone. The radiologist's equivalent of Wangensteen's "second look" appears to be a thoroughly justifiable procedure. An operative appraisal of supervoltage irradiation of the parametria is a commendable example, quite as important as the pathologist's final look at the area initially treated, even though the patient may have died of widespread metastases.

Local persistence of disease is evidence of local therapeutic failure. Local recurrence of disease is similar evidence, but the time required for reappearance of disease may be an indication of the rate of natural progress of the disease and an important prognostic sign for that particular individual.

With supervoltage equipment, the skin sensitivity is no longer a barrier to overtreatment of deeper structures. The subsurface complications of treatment can be extremely serious. There would appear relatively slight advantage in prolonging the life of the elderly cancer patient if the treatment creates a condition even less bearable than the original disease or its complications. The evaluation of the relative merits of heroic treatments and their complications can be made only by objective clinicians. Such evaluations impose a severe responsibility upon our senior and experienced colleagues.

THE PROPER FUNCTION OF A DEFINITION OF "CURE" IN CARCINOMA

In choosing a definition of "cure" of carcinoma, we have two principal aims in mind. First of these is a basis for the evaluation of the results of a *group* of patients treated. The second is to provide a basis for prognosis for the individual patient treated. These two objectives are not identical and need not be achieved by the same criteria.

In Nolan and Du Sault's Stage IV carcinoma of the cervix, the typical time of death is six months. The probability of living as long as five years and dying of the disease is less than 1 per cent. Under these circumstances the five-year symptom-free survival appears a reasonably safe criterion for cure.

In carcinoma of the stomach a dim picture also obtains, and with an estimate of five-year survival in 10 per cent of the operated on cases, five-year survival is a fair approximation of cure.

In contrast, symptom-free five-year survival rates in series of operated (and therefore selected) patients with carcinoma of the breast indicate a typical proportion of about 40 to 50 per cent surviving. Macdonald[8] has indicated that the most frequent cause of death in the five-year "cures" he studied is recurrent carcinoma of the breast. Five-year survival in this instance is a poor basis for future prognosis of the individual.

It would appear that only in those diseases which have a very short duration does the five-year survival have a reliable prognostic significance for the individual. As an evaluation of the effects of the treatment upon a group of patients, the five-year survival compilation throws away much of the information one works so hard to collect.*

* If only 5 per cent who die of a carcinoma survive more than five years, the odds are good that five symptom-free years suggest a cure. What does one say about the effect of treatment on the 95 per cent who died?

Much time and money is being expended on the problem of achieving "early" diagnosis. There is some small volume of data collected to indicate that the earliest detectable diagnosis may not be early enough. It seems possible that some carcinomas may disseminate widely at a time when they are too small for clinical recognition by any of our present methods.[3]* If these scattered instances of early dissemination can be confirmed by studies of others, it is conceivable that earlier diagnosis and earlier operation or radiation therapy will not necessarily cure more patients. This poses a problem in evaluation, since early diagnosis will provide at best, in such cases, palliative interference earlier in the natural history of disease. Any arbitrary criterion of cure, such as a five-year "cure" will reflect the longer total period of observation in the form of an increased "five-year cure" rate.

McKenzie[9] has shown that a 2.5 year extension of the life of every cancer patient would produce little change in the five-year survival rate with carcinoma of the stomach. (His data are from British Cancer Registration.) The five-year rate would increase from 4.6 to 6.8 per cent. In carcinoma of the lung it would increase from 1.5 to 3.0 per cent, in carcinoma of the cervix uteri from 32.0 to 44.0 per cent, and in carcinoma of the female breast from 31.0 to 49.0 per cent.

Such extension of 2.5 years is much greater than typical patient delay periods of three to nine months for most tumors, and indicates how little five-year survival rates would be influenced by very early detection or by very effective palliation. A more complete analysis, to include "cures," is needed. This cannot be accomplished reliably until we know how early tumors metastasize. With detailed knowledge of tumor doses necessary to eradicate local disease,† we could then calculate with some assurance the expected effect of early diagnosis.

SUGGESTED CRITERIA FOR PROPORTION CURED OF GROUPS OF PATIENTS

Boag[2] in England and Berkson and Gage[1] at the Mayo Clinic have independently arrived at what appear to be usable criteria of cure for carcinoma based upon the natural history of the disease. Their mathematical approaches differ, but, since the logical basis of these criteria is fundamentally similar, both will lead to estimates of proportions cured which should be in reasonable agreement. Since the five-year cure rate will consistently overestimate the proportion of patients cured, this proportion, when evaluated in terms of the natural history of disease, using either Boag's or Berkson and Gage's criteria, will result in substantially lower proportions of "cures." For example, in carcinoma of the breast, in which the "five-year cure rate" was approximately 40 per cent, Boag's calculation of proportion cured was about 25 per cent, a considerably more realistic figure.‡

Both of these methods have the overwhelming advantage of enabling the investigator to predict, in advance of the time of death of all his patients, the ultimate outcome of all his series. In addition, he obtains an estimate of a typical survival of those who will die of carcinoma—in fact, a distribution of the survival times of all those who will die. The confidence limits on these estimates permits reliable comparisons with the results of others. Unlike the "five-year cure," neither the Boag nor the Berkson and Gage method provides any estimate or prognosis for an individual. For the practicing therapist, this is a tremendous handicap, particularly since the "five-year cure" is frequently unreliable. In general, the greater proportion of five-year cures, the less reliable this criterion will become.

* If one assumes geometric growth by division of each cell present and growth rates are uniform, the typical tumor has lived over half its lifetime before it becomes large enough to be discovered.

† Data of this type controlled by pathologic studies are remarkably scanty except for skin cancer.

‡ This lower proportion cured makes allowance for those cases which will die after five years.[8]

CRITERIA OF CURE FOR THE INDIVIDUAL

As in the problem of cure of the group, a reasonable criterion of the cure for the individual must be based upon the natural course of the patient's tumor.

There are some previous criteria which may be of value. The diagnosis itself, *i.e.*, the diagnosis of malignant choriocarcinoma, implies a much shorter survival for the woman than a diagnosis of cancer of the breast. Clinical staging may be, in some instances, a reflection of the inherent growth rate of tumor rather than the patient delay to detection of the tumor.

In one series[12] of patients with carcinoma of the stomach, resected patients had typically twice the patient delay of inoperable patients. One might suggest that delay improved prognosis.* This is more readily explained if longer persistence of symptoms implied a more slowly growing tumor. If tumor growth rates were constant and we knew the time of origin of a tumor, a tumor should take no longer to recur if inadequately treated than it took to reach a diagnostic size in the first instance. If one assumes that all Wilms's tumors began in utero and that the time of diagnosis is a reflection of the growth rate of the tumor, then the maximum time for recurrence of a tumor should be the age at diagnosis plus nine months. In a series[3] of Wilms's tumors so studied, it was found that all known recurrences did occur within this interval. We have informal information indicating that recurrences of neuroblastomas of childhood have followed a similar pattern.[7]

It would then appear useful for others to examine their material on tumors of early childhood to see if recurrences occurred later than the age at diagnosis plus nine months from the time of therapy. If no exceptions are found for those tumors which might be congenital in origin, this simple criterion may prove a useful definition of cure for the *individual* patient. It requires no lengthy calculations and appears at this time to be based upon the natural history of disease in that particular patient. Obviously, this type of study cannot be extended to many adult tumors until we know more about the origin of tumors in the adult. Such studies rest on the assumption that tumor growth rates are uniform. We would anticipate considerable difficulty in adapting these concepts to the endocrine-dependent tumors, such as carcinoma of the breast or prostate.

PROGNOSIS FOR THE INCURABLE PATIENT

It has been estimated that approximately 90 per cent of all patients treated by the radiotherapists are "incurable." A high proportion of these are capable of some improvement, or at least arrest, of their local disease by adequate roentgen therapy.

The first problem is to select those in whom disease is no longer localized and are, therefore, "incurable" by any present means. The internist, the biochemist and the diagnostic radiologist will have continuing contributions to make in this problem. Ideally, a treatment plan for the incurable patient is one which produces the maximum palliation with the least morbidity, the least risk of complication and the smallest sacrifice of useful time and money remaining to the individual. Objective numerical data on what is meant by palliation appear relatively infrequent, and it would seem that much effort can be properly expended to define an optimal balance between minimal radiation and maximal effect for a wide variety of diseases.

THE USE OF GROWTH RATES IN TREATMENT PLANNING FOR THE INDIVIDUAL

In some instances an estimation of the growth rate of a tumor can be made either from serial determinations of its measured size, or from the measured size of pulmonary metastases. On the basis of a simplified assumption that all cells in the tumor are capable of division, it has been calculated that the range of time required

* The confusion of "association" with "cause" could lead similarly to the conclusion that wearing straw hats "causes" malaria.

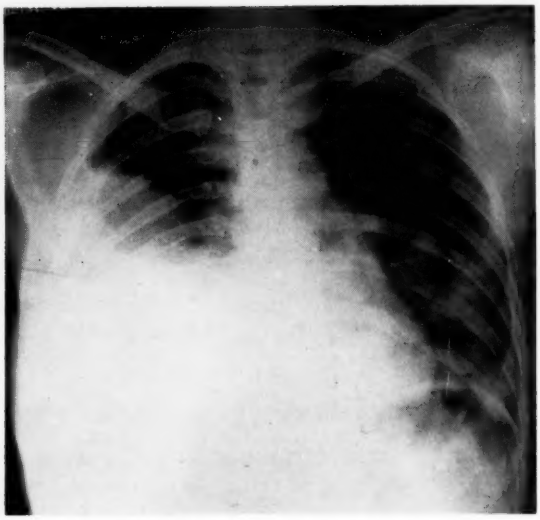

FIG. 1

for each cell to divide and become two cells, thus doubling the volume of the tumor, ranges from approximately 7 days for "explosively growing tumors" to as long as 120 days for slowly growing tumors.

If a tumor is discovered at the size of 1 cm., all the cells in that tumor and their progeny can divide only about 12 times more until the total tumor exceeds 8 kg. in weight. Depending on its location, as a rough rule of thumb, very few malignant tumors ever reach a total mass much greater than 5 kg. before killing the patient.

If some estimate of the time required for the tumor to double in *volume* can be made from serial measurements, serial roentgenograms, or even from the patient's history, this may be of value in planning treatment appropriate to the patient's disease.

REPORT OF A CASE

C.L.R., a thirty-two year old colored housewife, was perfectly well until September of 1955, when a small firm mass was noted on the right chest wall below the axilla. In October, 1955, this lesion and two underlying ribs were removed at another hospital.

She was seen at the Jefferson Davis Hospital on January 4, 1956, with findings compatible with an acute pneumonia and right hydrothorax. A 1×5×5 cm. nodule was noted adjacent to the operative site which the patient stated had been noticed first three weeks previously.

Review of systems disclosed only a 6-pound weight loss following anorexia of two weeks' duration. Physical examination was noncontributory except for the findings of the right thorax.

The patient was admitted to the hospital and the thoracic recurrence biopsied. The pathologic diagnosis was "fibrosarcoma, probably periosteal." Thoracentesis yielded a bloody effusion but no malignant cells were identified.

Admission laboratory work disclosed hemoglobin level of 7.0 grams per 100 ml. and a leukocyte count compatible with acute infection.

Roentgenograms disclosed a right pleural effusion, metastatic nodules in both lung fields, and local erosion of ribs adjacent to the operative site (Fig. 1). Skeletal survey was negative except for these lesions. Hepatic enlargement was noted on films of the abdomen.

A study of serial chest films disclosed a "doubling time" of ten days for the pulmonary metastases. A line drawing of the admission chest film and the plot of serial pulmonary metastases are reproduced in Figure 2.

The patient's course was steadily downhill. Palliative local radiation to the right hemithorax (250 kv. half-value layer 3.0 mm. Cu to opposing 14×20 cm. fields, 150 r per day midplane tumor dose to a total of 900 r) produced no effect and was, therefore, discontinued. She died on January 26, 1956.

COMMENT

From the truncated case report presented above, there are four clear indications of extremely rapid growth rate. The first of these is the occurrence of the subcutaneous nodule in an area which was evidently "surgically clean" two and one-half months previously. If the patient's history could be believed, a tumor mass which would grow from a detectable nodule to a 5×5×1 cm. mass in two weeks is rapidly proliferating. The finding of metastatic bone disease in an area which had not shown such disease three months before is an indication of rapid progression. The estimate of growth rate from serial measurements of the same nodule is a more quantitative verification of the obvious clinical impression from the above findings. The histo-

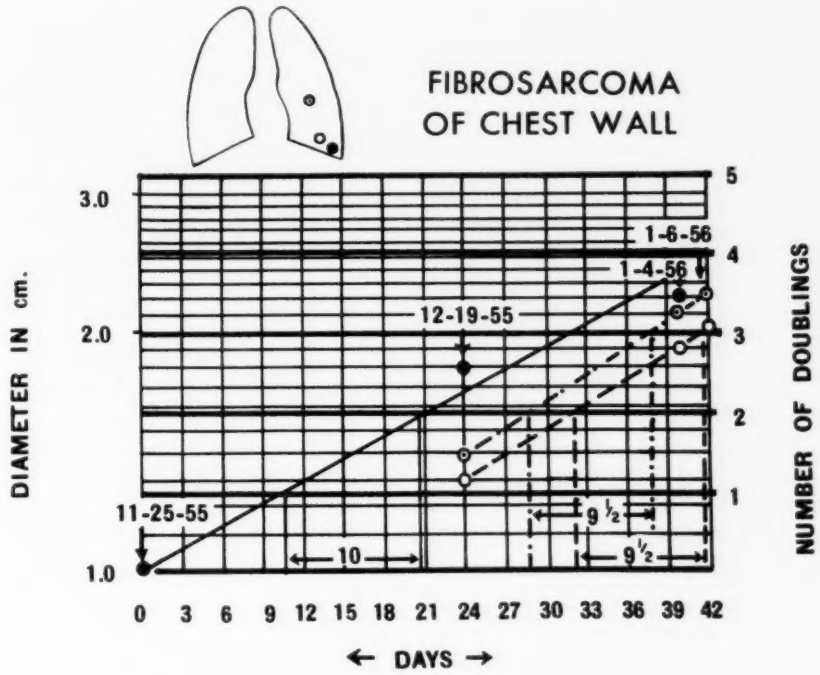

Fig. 2

logic diagnosis of fibrosarcoma carries no particular prognosis in most instances, since this may be either very slowly or very rapidly growing.

While the histology of the tumor was initially unknown, the review of serial films and the patient's history clearly indicated that the rate of growth and the extent of disease was such that only minimal palliative treatment at irradiation levels which would not worsen the patient's condition could be justified.

In contrast, the growth rate of a fibrosarcoma[3] of the popliteal space, as measured in serial chest films, was so slow that at least four years was required for a small pulmonary metastasis to reach a size capable of producing dyspnea. In such an instance, surgical removal or intensive radiation therapy to an isolated metastasis, or several metastases, might be justified.

Further instances in which this concept might prove of value might be in carcinoma of the thyroid or kidney; or sarcoma producing pulmonary metastases. Since most of these cases are initially operated on, the worst possible prognosis would be gained by the assumption that the trauma of surgery set loose a tumor embolus which lodged in the lung and grew to the size of first detection between the time of surgery and that film. This could be followed briefly for further increase in size, or one might assume that 20 doublings were required to reach 1 cm. The time interval divided by 20 would then give an estimate on the "high side." If the growth rate still appeared relatively slow, *i.e.*, of the order of 30 days' doubling time, local therapeutic measures for known metastases might then be reasonably undertaken. Measurable bone lesions might similarly be studied. If the growth rate appeared very rapid on the basis of this estimation, one would have little to lose by further observation of an asymptomatic pulmonary metastasis or a nonpainful bony metastasis in a noncritical area, such as the ilium.

SUMMARY

A few problems of the evaluation of the results of cancer therapy have been discussed briefly. Acceptable solutions to the

problems of computing the proportion of the patients cured by any type of cancer therapy appear at hand. Such criteria are of no value as a basis for estimation of the prognosis of the individual. Further study on methods of estimating the natural course of disease in an individual will be required to provide a sound basis for prediction of that patient's prognosis, cured or uncured, and for the most rational planning of palliative or curative therapy.

Harold Tivey, M.D.
1200 M.D. Anderson Blvd.
Houston 25, Texas

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THE EFFECT OF ROENTGEN-RAY QUALITY ON BONE GROWTH AND CORTICAL BONE DAMAGE*

By LEONARD ROSENTHAL, M.S.,† *and* JAMES F. MARVIN, PH.D.
MINNEAPOLIS, MINNESOTA

MEASUREMENT of roentgen radiation with the thimble ionization chamber (r-meter) yields information on the energy dissipation in soft tissue (water equivalent). Bone, because of the presence of calcium and phosphorus, may be the source of more secondary electrons and consequently may absorb more energy than the soft tissue. Juris,[2] and Stenstrom and Marvin[3] have shown by ionization measurements with bone chambers that this energy dissipation in bone varies with the wavelength of the roentgen rays; this dependence has been determined for qualities of radiation used in radiation therapy. The present experiments were planned to correlate the biologic effect and the bone ionization study.

The physical study,[3] with bone ionization chambers, showed that ionization in bone was four times that in soft tissue (lucite ionization chamber) for radiation with half-value layer (hvl.) 0.4 mm. copper; ionization in bone was twice that of soft tissue for radiation with half-value layer 2.4 mm. copper. Absorption of energy in the bone irradiated with 0.4 mm. copper hvl. radiation could be expected to be double that in bone irradiated with the harder 2.4 mm. copper hvl. radiation, if equal soft tissue doses (roentgens) were delivered.

LITERATURE

Gall, Lingley, and Hilchen[1] compared changes in mammalian tissues irradiated with roentgen rays of half-value layers of 0.75 and 10.5 mm. copper. No striking differences were shown in the histologic studies of the epiphysial cartilage plate. This might be expected as this cartilage does not differ in atomic number from the soft tissue.

Woodard and Spiers[4] compared effects of radiations of hvl. 0.75 mm. Cu and 3.8 mm. Pb. (about 10 mm. Cu) on the suppression of alkaline phosphatase in the tibia of the mouse. Deactivation was found to be 1.35 times greater for the softer radiation. Not all the alkaline phosphatase, however, is found in the calcified bone. Much is found also in the region of the epiphysial cartilage.

EXPERIMENTAL METHODS

The factors used for the hard radiation were 220 kv. (peak), 15 ma., Thoraeus II filter, hvl. 2.4 mm. copper, with a target to bone distance of 26 cm. The dose rate was 108 r per minute at the center of the 3 cm. diameter cone. The factors for the softer radiation were 140 kv. (peak), 5 ma., filter $\frac{1}{4}$ mm. Cu plus 1 mm. aluminum, with a target to bone distance of 16 cm. The dose rate was 76 r per minute in the center of the same 3 cm. diameter cone.

Male rats of the same strain were irradiated at the age of 35 days. The animals anesthetized with nembutal (1 mg. per 40 mg. body weight) were securely tied face down on an empty cardboard box to reduce backscatter. The hind legs were spread so that the unirradiated tibia received less than 0.6 per cent of the dose to the irradiated tibia (hvl. 2.4 mm. Cu) or less than 0.15 per cent of the dose (hvl. 0.4 mm. Cu).

Serial roentgenograms were taken to determine bone growth. The rats anesthetized with ether were spread-eagled and securely taped on the cassette to insure close contact of knee and ankle avoiding errors in measurement of tibial lengths. The factors used were 38 kv. (peak), 100 ma., 1/20 sec. at 50 inch focal skin distance.

The rats were fed Purina Fox checkers with food and water available *ad libitum*.

Supported in part by grants from the American Cancer Society and the Atomic Energy Commission.
* From the Department of Radiology, University of Minnesota Hospitals, Minneapolis, Minnesota.
† Now at McGill University, Montreal, Canada.

TABLE I

TIBIAL LENGTHS IN MILLIMETERS AT VARIOUS INTERVALS FOLLOWING IRRADIATION OF THE RIGHT KNEE. hvl. 0.4 MM. Cu, 1,000 r (LEFT TIBIA SERVED AS CONTROL)

Days Post-irradiation	Rat A		Rat B		Rat C		Rat D	
	Left Tibia	Right Tibia	Left Tibia	Right Tibia	Left Tibia	Right Tibia	Left Tibia	Right Tibia
0	27.0	26.8	26.3	26.3	26.8	26.9	25.0	25.0
13	31.0	30.2	30.0	29.7	31.7	30.4	30.1	29.5
27	34.2	32.6	34.2	32.5	34.5	32.5	33.3	31.8
41	35.8	34.0	35.8	33.8	35.6	33.7	34.9	33.3
87	37.8	35.5	38.2	35.5	37.8	35.2	37.5	35.1
% of normal growth rate at 87 days	80.5		77.3		75.5		80.8	

They were housed 4 per cage (Experiment 1) or 3 per cage (Experiment 2) at a constant temperature.

Experiment 1. This experiment involved irradiation of the tibial femoral region of the right leg only with 1,000 r. Two groups of rats, each consisting of 4 male litter mates, were irradiated at the age of 35 days. One group received radiation of hvl. 0.4 mm. copper; the other group, radiation of hvl. 2.4 mm. copper.

The absolute tibial lengths were measured with a micrometer caliper from the roentgenograms taken the day before irradiation and serially after irradiation. The percentages of normal growth during stated periods are listed in Tables I and II.

The average 0 to 87 day growth retardation was 78.5 per cent (Table I) for animals receiving the softer radiation and 76.5 per cent (Table II) for animals receiving the harder radiation. The probability that the two values could arise by random sampling of rats is 0.27. The hard and soft radiations thus appear equally effective in producing bone growth retardation.

Experiment 2. This experiment involved irradiation at the age of 35 days of both knees of each rat with 1,000 r the right knee with hard rays (hvl. 2.4 mm. copper) and the left knee with soft rays (hvl. 0.4 mm. copper). Tibial measurements, taken from the roentgenograms are given in Table III. No striking differences in stunting of bone

TABLE II

TIBIAL LENGTHS IN MILLIMETERS AT VARIOUS INTERVALS FOLLOWING IRRADIATION OF THE RIGHT KNEE. hvl. 2.4 MM. Cu, 1,000 r (LEFT TIBIA SERVED AS CONTROL)

Days Post-irradiation	Rat E		Rat F		Rat G		Rat H	
	Left Tibia	Right Tibia	Left Tibia	Right Tibia	Left Tibia	Right Tibia	Left Tibia	Right Tibia
0	24.5	24.5	25.1	25.1	24.8	24.8	25.5	25.5
13	27.8	27.0	29.0	28.1	28.5	27.7	29.7	29.1
27	30.8	29.2	31.4	29.9	30.8	29.5	32.0	31.8
41	33.1	30.6	33.7	32.0	32.0	30.4	33.2	31.8
87	35.7	32.8	35.0	32.7	34.0	31.8	35.0	33.2
% of normal growth rate at 87 days	74.0		76.9		74.2		81.0	

TABLE III

TIBIAL LENGTHS IN MILLIMETERS FOLLOWING IRRADIATION OF THE KNEES. THE RIGHT KNEE RECEIVED 1,000 r AT 2.4 MM. Cu hvl. THE LEFT KNEE RECEIVED 1,000 r AT 0.4 MM. Cu hvl.

Days Post-irradiation	Rat 1		Rat 2		Rat 3		Rat 4		Rat 5	
	Left Tibia	Right Tibia	Left Tibia	Right Tibia	Left Tibia	Right Tibia	Left Tibia	Right Tibia	Left Tibia	Right Tibia
0	25.9	25.9	25.5	25.5	25.4	25.4	25.9	25.9	25.1	25.1
17	31.0	31.1	31.2	31.2	30.2	30.0	30.4	30.4	29.8	30.0
26	32.5	32.8	32.8	32.8	31.5	31.5	31.8	31.8	31.8	32.0
40	34.1	34.5	34.3	34.2	33.2	33.2	33.2	33.5	33.7	34.0
67	34.3	35.6	—	—	—	—	—	—	35.4	35.6
89	36.7	36.5	36.3	36.3	35.6	35.6	34.8	35.0	36.0	36.2

growth appear between the two qualities of radiation.

Experiment 3. This experiment involved the histologic study of cortical bone damage. The criterion for evaluation of the radiation damage was the number of empty lacunae or lacunae filled with nuclear debris.

A total of 40 rats were studied. Only one tibia of each rat was irradiated; the other tibia served as control. Three rats were used for each quality of radiation at doses of 500 r, 1,000 r, 1,500 r, and 2,000 r, delivered in a single treatment. Rats were sacrificed at one, two, and three weeks. Three rats were used for each quality of radiation at doses of 6,000 r and 9,000 r, delivered in divided doses, 3,000 r per day, on two and three successive days. Rats were sacrificed in roughly two, three, and seven weeks. Two rats were used for each quality at doses of 12,000 r. delivered in divided doses of 3,000 r, on four successive days. Rats were sacrificed at two and four weeks.

The following technique was used for the histologic examination: 1. the tibias were disarticulated, cleansed of muscular tissue and fixed 12 to 24 hours in 10 per cent formalin; 2. the bone was decalcified not less than three days nor longer than eight days in solution consisting of 10 grams Winthrop-Stearns ion-exchange resin (Win-3,000) in 80 cc. of 20 per cent formic acid; 3. the bone was dehydrated 6 to 12 hours each, in 80 per cent, 95 per cent and absolute alcohol, successively; 4. the bone was cleared in xylol, embedded in paraffin, sectioned, and stained in hematoxylin and/or eosin.

RESULTS

The damage produced in the cortical cells can be roughly evaluated as follows:

1. No damage is detected at 2,000 r or less. Compare Figure 1, normal, with Figure 2, 2,000 r (hvl. 0.4 mm. Cu).
2. No damage is evident in Figure 3, 6,000 r (hvl. 2.4 mm. Cu).
3. Extensive damage appears in Figure 4, 6,000 r (hvl. 0.4 mm. Cu).
4. Damage apparent in Figure 5, 9,000 r (hvl. 2.4 mm. Cu) is not as severe as in Figure 4, 6,000 r (hvl. 0.4 mm. Cu).
5. Complete osteocyte destruction is evident in Figure 6, 9,000 r (hvl. 0.4 mm. Cu) and in Figure 8, 12,000 r (hvl. 0.4 mm. Cu).
6. Damage evident in Figure 7, 12,000 r (hvl. 2.4 mm. Cu) exceeds that of Figure 5, 9,000 r (hvl. 2.4 mm. Cu), but is less than that of Figure 6, 9,000 r (hvl. 0.4 mm. Cu). A rough general cell count indicates less damage is shown at this dose than in Figure 4, 6,000 r (hvl. 0.4 mm. Cu), although Figures 4 and 7 show about equal damage.
7. No evidence was found seven weeks after irradiation of any repair of radiation damage to the cortical cells.

FIG. 1. Normal tibia of rat (×230).

FIG. 2. 2,000 r, 0.4 mm. Cu hvl.

FIG. 3. 6,000 r, 2.4 mm. Cu hvl.

FIG. 4. 6,000 r, 0.4 mm. Cu hvl.

FIG. 5. 9,000 r, 2.4 mm. Cu hvl.

FIG. 6. 9,000 r, 0.4 mm. Cu hvl.

FIG. 7. 12,000 r, 2.4 mm. Cu hvl.

FIG. 8. 12,000 r, 0.4 mm. Cu hvl.

SUMMARY

Roentgen rays of two qualities, 0.4 mm. copper hvl. and 2.4 mm. copper hvl., were compared with regard to their effectiveness in retarding longitudinal growth and in producing histologic change in the cortical bone of the rat tibia.

No marked difference was found in retardation of longitudinal growth of the tibia. These two qualities of radiation would be expected to act similarly on longitudinal bone growth as the atomic number of the epiphysial cartilage is much closer to that of soft tissue than of bone.

Roentgen rays of hvl. 0.4 mm. copper produce twice the damage in cortical bone shown by roentgen rays of hvl. 2.4 mm. copper in very close agreement with previously published data on ionization in bone. Criterion of damage was the number of empty and nuclear-debris laden lacunae in the histologic preparations.

James F. Marvin, Ph.D.
University of Minnesota Hospitals
Minneapolis 14, Minnesota

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MORTALITY OF RHESUS MONKEYS AFTER SINGLE TOTAL BODY IRRADIATION

By ULRICH K. HENSCHKE, M.D., Ph.D., *and* JOSEPH L. MORTON
NEW YORK, NEW YORK

A BASIC figure for the evaluation of the hazards of ionizing radiation is the mortality after single total body irradiation. For many animal species good figures are available. Rajewsky[8] (1954), on the basis of a recent survey of the literature, gives the following values for the LD 50/30 (lethal dose for 50 per cent of the animals within 30 days): goat 350 r, guinea pig 400 r, dog 400 r, swine 430 r, rat 600 r, burro 650 r, rabbit 800 r, and hamster 900 r.

From these animal values an estimate of the LD 50/30 of man is difficult, because the reasons for the marked species differences are unknown. Studies with animals, which are closely related to man, appear therefore desirable. The most readily available animals in this respect are rhesus monkeys.

Two studies on the mortality of rhesus monkeys after total body irradiation have been reported. Both were carried out with a small number of animals and the results were considered by the authors as tentative only. Dowdy[1] (1949) estimated the LD 50/30 as 500 r, while Eldred and Towbridge[2] (1954) estimated the LD 50/30 as 600 r. In Eldred and Trowbridge's study 2 of 8 or 25 per cent of the animals died at 400 r, 3 of 7 or 43 per cent at 600 r, 9 of 10 or 90 per cent at 700 r, and 5 of 6 or 83 per cent at 800 r.

On the initiative of the Public Health Service, a more accurate determination of the LD 50/30 of rhesus monkeys was assigned to the Ohio State University. The studies on the LD 50/30 were terminated in June, 1955, when it was felt that sufficient information had been accumulated. This publication reports in detail on the irradiation set-up, the dosimetry, the mortality data and the LD 50/30. The pathologic findings in the same group of rhesus monkeys have already been reported by Schlumberger and Vazquez[9] (1954).

ANIMALS

The monkeys used in this study were rhesus macaques (Macaca mulatta). They were imported from northern India and were purchased from the Trefflich Bird and Animal Company, Inc., 228 Fulton Street, New York, New York. The animals were of both sexes in approximately equal distribution. The age was estimated at one and one-half to three years on the basis of roentgen studies of the jaws, which showed unerupted teeth. In the rhesus monkey, puberty begins at about three years, but reproduction is not regular until the age of four and one-half years. All animals were tuberculin tested, but owing to lack of space it was not always possible to isolate all new arrivals.

The animals were housed in cage of heavy sheet metal measuring 2×2×2 feet; only the front and the top were fenestrated. Two monkeys had to be kept in each cage. It was necessary to have cage mates of approximately equal size and temperament to avoid injury and malnutrition of the weaker. The animal quarters were in an old operating room, which measured 22×15 feet and had a high ceiling. It was air conditioned and was kept at 72° F. Large windows stretching across one entire wall provided adequate daylight.

The monkeys were fed three times each day. In the morning and late afternoon, they were fed a moist mash made by adding water to the dehydrated Okatie Farm Primate Diet; at noon they received an apple or an orange. The Okatie Farm Primate Diet is composed of ground wheat, soy bean meal, and dry powdered milk to which alfalfa meal, sugar, bone meal,

calcium carbonate, sodium chloride, viosterol, thiamine, niacin, folic acid, riboflavin, pyridoxine, and calcium pantothenate have been added.

According to a special stipulation of the grant, no other diagnostic or therapeutic procedures were to be carried out on those animals which were included in the study of the LD 50/30. The monkeys were therefore taken out of their cages only at the time of irradiation.

POSITIONING OF ANIMALS DURING IRRADIATION

Since irradiation times up to 45 minutes were required and since the position of the animals must be maintained within narrow limits, a good fixation was of importance. After trials with fixation on a chair similar to the arrangement of Eldred and Trowbridge[2] (1954) and attempts of immobilization in a plastic form, a satisfactory arrangement was found by putting the monkey into a perforated plastic cylindrical cage. These were made from commercially available polyethylene tubes containing carbon black with an inside diameter of 6 inches, a wall thickness of 5/16 inch and a specific gravity of 0.85. The cylinders measured 20 inches in length and were perforated with holes of $\frac{1}{2}$ inch diameter. Two holes were drilled per square inch so that 40 per cent of the area consisted of holes. Masonite disks of 3/16 inch thickness were inserted into both ends of the cylinder to prevent escape of the monkey.

Figure 2 shows a roentgenogram of the monkey in the cylindrical perforated cage. Insertion of the monkey into the cage was done head first. This is not too difficult and once in the cage, the monkey appeared to be quite comfortable and did not struggle. Insertion and release of the monkey was done in the animal's quarters and the monkeys were carried safely and inconspicuously in the cages to the hospital radiologic department for irradiation.

IRRADIATION ARRANGEMENT

Figure 1 shows schematically the irradiation arrangement. A regular roentgen therapy machine served as the roentgen ray source. It was a Westinghouse Quadrocondex constant potential machine with a detached oil cooled tube and was operated at 250 kv. and 15 ma. A regular roentgen therapy filter of 0.5 mm. copper and 1.0 mm. aluminum was used; it was located 7 cm. from the anode. An additional special compensating filter, which will be described in detail in the next paragraph, was located at a distance of 12 cm. from the anode. The cage with the monkey was positioned at 100 cm. distance from the focus of the roentgen tube. The cage was suspended by wires in air from a steel frame ordinarily used for bed screens in the hospital. A rotating joint was provided in the upper suspension wire. The lower suspension wire was connected to the axis of a reduction gear, and was rotated by aid of an electric motor with a speed of approxi-

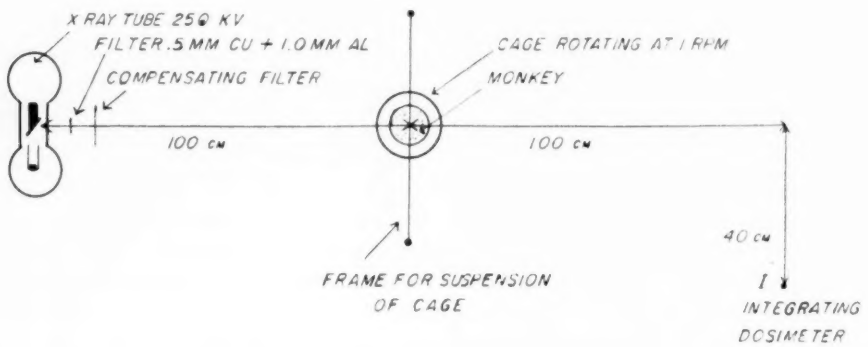

FIG. 1. Arrangement for monkey irradiation.

mately one revolution per minute. One hundred cm. behind the cage and 40 cm. to the side of the central beam, an integrating dosimeter was located, which will be discussed under "Dosimetry."

Figures 3 and 4 show the design as well as the effect of the compensating filter. In Figure 3 the relative doses at a focus distance of 100 cm. and in a plane perpendicular to the main axis of the roentgen ray beam are given. For comparison, the outlines of the cage and of a monkey in the cage are shown. The dose differences in the vertical axis are due to the inverse square dependence of the dose; the dose differences in the vertical axis are due to the anode heel effect. The dose varies by 8 per cent within the space occupied by the cage.

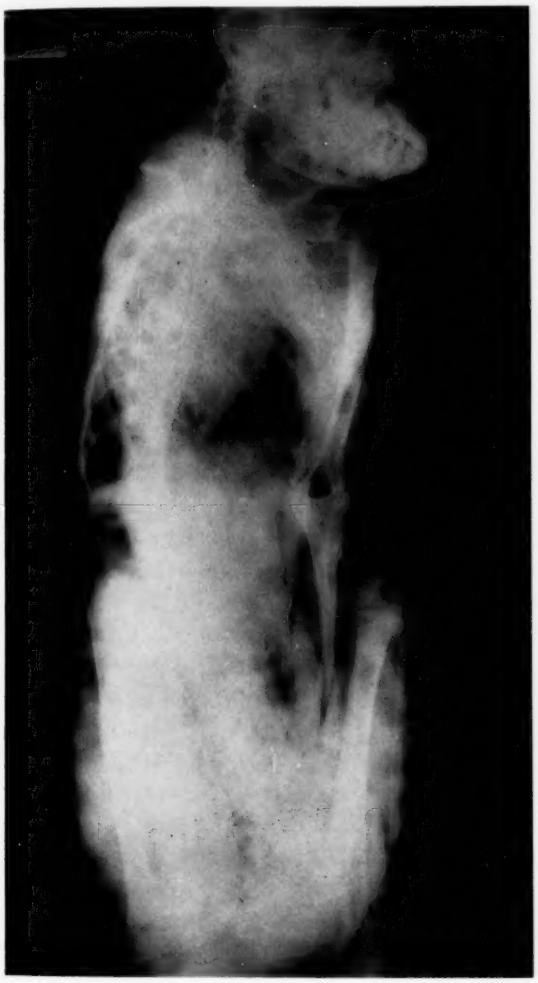

Fig. 2. Roentgenogram of a monkey in the perforated polyethylene cage, which was used for accurate positioning of the animals during irradiation.

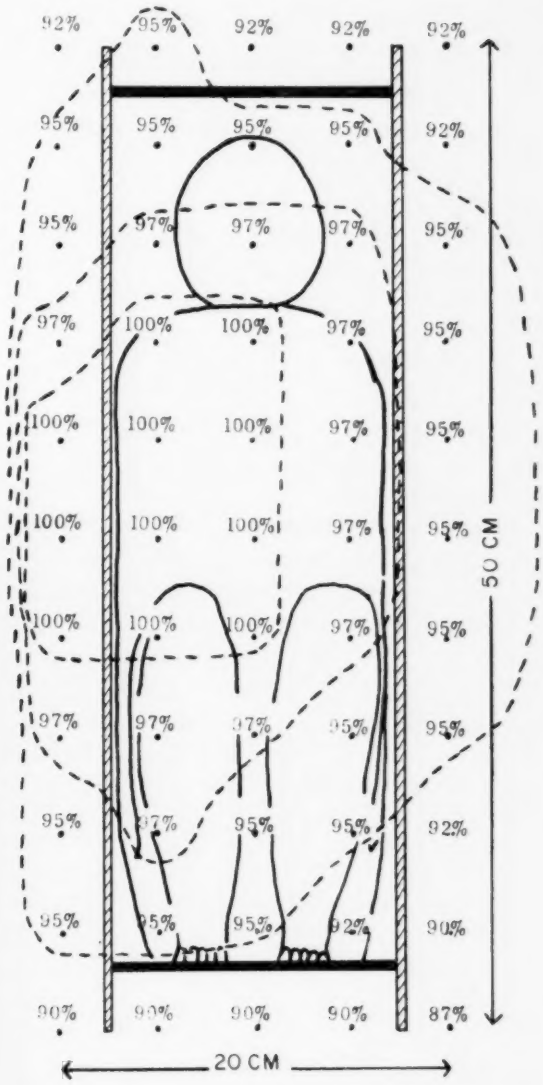

Fig. 3. Relative doses at 100 cm. focus distance. Dotted lines show the shape of the three layers of the copper compensating filter.

In order to achieve a more uniform radiation field, a compensating filter was constructed. A method similar to that described by Greenfield and Hand[7] (1951) was followed. For ease of reproduction a simple design with only three copper sheets was chosen. The shape of each of these filters is shown in dotted lines in

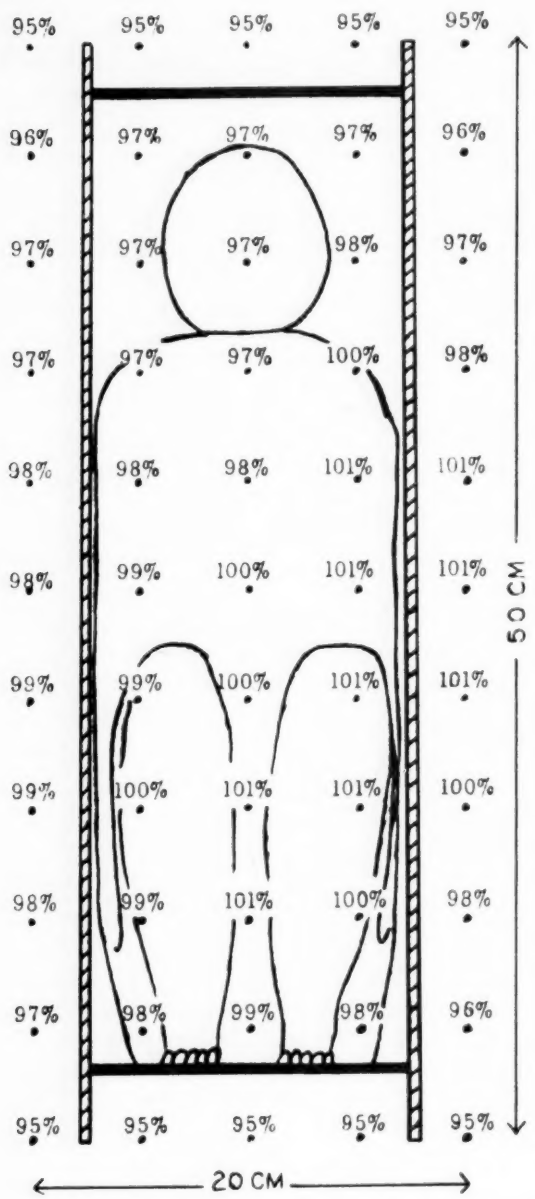

FIG. 4. Relative dose rates at 100 cm. focus distance with the compensating filter.

Figure 3. The secondary radiation from the copper filter was absorbed in an additional 1 mm. aluminum filter attached on the side away from the roentgen tube. Figure 4 shows the improvement in the relative dose distribution accomplished with this compensating filter. The dose varies now only by 4 per cent within the space occupied by the cage. For the purpose of this study, this appeared acceptable.

Half-value layer measurements with copper filters were carried out in the center and in the periphery of the field. Due to the greater thickness of the compensating filter in the middle of the field, a higher half-value layer was expected. The measurements showed in the center of the field a first half-value layer of 1.8 mm. copper and a second half-value layer of 3.0 mm. copper. In the periphery of the field, the first half-value layer measured 1.7 mm. copper and the second half-value layer 3.0 mm. copper. There is thus the expected difference in the first half-value layer between center and periphery of the radiation field. However, its degree appears insignificant. The dose rate in the rotational axis was on the average 22 r/min.

DOSIMETRY

For the determination of the total dose given to each animal an integrating dosimeter was used. A Siemens Universal dosimeter was chosen, which consists of a thimble chamber connected to a quadrant electrometer by a long flexible cable. A condenser is charged by the ionization current in the thimble chamber and the charge of the condenser, which is proportional to the total dose, is measured directly with the quadrant electrometer. Compared with simple condenser type dosimeters such as the Victoreen, the Siemens dosimeter has the advantage that the total dose given can be read directly at any time during the roentgen exposure. This makes it possible to switch off the roentgen ray machine when a certain dose such as 300 r or 500 r has been reached. This integrating dosimeter was placed in a position about 200 cm. from the focus and 40 cm. sidewards from the central beam as indicated in Figure 2. The exact position is not critical as long as it remains unchanged after the calibration.

The calibration of the integrating dosimeter was carried out before and after irradiation of each monkey group by comparison with a Victoreen 100 r condenser chamber. The latter was placed inside a 10 cm. diameter masonite phantom

in the rotating cage. After correction for pressure and temperature, a factor was established between the chamber in the phantom and the integrating dosimeter, which was usually about 4.2. The Victoreen chamber and instrument were calibrated at the beginning and at the end of the present series at the Bureau of Standards, Washington, D.C.

The position of the integrating dosimeter indicated in Figure 2 was chosen for two reasons: Firstly, the highest available scale on most integrating dosimeters is 250 r. Since doses up to 900 r were given to some monkeys, a reduction factor was necessary and such a factor is most easily realized by distance. Secondly, the integrating dosimeter must be far enough from the animals so that the radiation scattered from the animal to the dosimeter is insignificant. If the integrating dosimeter was placed 20 cm. beside the rotational cage, the dose was 3.4 per cent higher when a cylindrical masonite phantom 15 cm. high and 8 cm. in diameter was in the cage than when the cage was empty. If the integrating dosimeter was in the position indicated in Figure 2, no increase of the dose was demonstrable when the phantom was inserted into the cage. This was therefore considered a suitable position.

In the standard calibration procedure, the dosimeter in the axis of rotation was placed into a phantom 15 cm. high and 8 cm. in diameter. This phantom had a central bore of 1.6 cm. diameter for insertion of the 100 r condenser chamber of the Victoreen dosimeter. The phantom was built of vertically laminated masonite and had a specific gravity of 1.018.

The question was explored whether, in monkeys of various sizes, a difference in tissue dose would occur due to the differences in absorption and scatter. Measurements with the 100 r condenser chamber inside the empty cage (air dose) and inside the phantom in the cage (tissue dose) did not show definite differences. It was therefore assumed that, for this particular rotational arrangement, the size of the monkeys within the ordinary limits has no significant influence on the tissue dose and that the tissue dose is equal to the air dose.

RECOMMENDATIONS FOR IRRADIATION OF RHESUS MONKEYS

One purpose the the Public Health Service grant was to develop an irradiation arrangement for rhesus monkeys which can be easily duplicated wherever a 200–250 kv. roentgen ray therapy unit is available. This arrangement was intended to serve as a model for all other institutions which are carrying out other irradiation studies with rhesus monkeys.

On the basis of our experience, we recommend the set-up shown in Figure 2 together with the cylindrical perforated polyethylene cages and the compensating filter described in the preceding paragraphs. As an inexpensive set for dosimetry, we advise a Victoreen condenser dosimeter with two 250 r chambers. The first chamber is used as integrating dosimeter during the monkey irradiation and is placed in position 1, as shown in Figure 2. The second chamber is used for the calibration of the first chamber. For this purpose, the second chamber is suspended in air in the middle of the polyethylene cage. For the calibration, irradiation is carried out during rotation of the cage, delivering about 200 r to the second chamber in the middle of the cage. During this irradiation, the first chamber at position 1 is also exposed. On the basis of the readings of the two chambers, a calibration factor is established, which will be close to 4.

During irradiation of the animal, only the first chamber at 1 is exposed. The approximate dose is predetermined from the dose rate previously measured by the second chamber in the polyethylene cage. The exact dose is determined at the end of the monkey irradiation by the reading of the first chamber at 1 multiplied by the calibration factor. The use of a direct reading dosimeter instead of the Victoreen condenser chamber at position 1 is more convenient, but these instruments are more expensive and need more attention and

understanding than the economical and rugged Victoreen condenser dosimeter.

EFFECTS OF TOTAL BODY IRRADIATION IN RHESUS MONKEYS

The clinical and pathologic findings in our group of monkeys have been reported in detail by Schlumberger and Vazquez[9] (1954). Most findings were similar to observation in other species.

Symptoms after irradiation were anorexia within 24 hours in all animals. At and above 500 r, diarrhea was noted. At and above 800 r, the diarrhea was severe and watery and occasionally blood streaked. No vomiting was observed. This is in contrast to the findings of Eldred and Trowbridge[2] (1954), who saw short vomiting episodes immediately after irradiation in all their rhesus monkeys except in the 700 r group, which were not fed preceding the irradiation. All of our animals were denied food for 4 hours preceding the irradiation. This may explain the total absence of vomiting in our series. Epilation was found after 12 days at doses above 500 r.

At autopsy, performed usually shortly after death, the most important finding was the aplasia of the bone marrow. However, beginning regeneration was observed after only 18 days in the one animal dying after 300 r. After 400 r, the aplasia was less marked than with the higher doses. The spleen, the lymph nodes and the lymphoid tissue in the gastrointestinal tract showed widespread destruction of the lymphocytes in all animals. Regeneration was noted not earlier than 180 days. In some monkeys surviving over 300 days, pronounced follicular hyperplasia resembling giant follicular lymphoma was observed. The gastrointestinal tract showed petechiae at and above 300 r and ulceration at and above 500 r; the changes were most frequently seen in the colon. A striking finding was necrotizing ulceration of the gingiva, which occurred at and above 400 r and was encountered in 9 of the 10 animals of the 700 r group, which died 11 to 15 days after exposure. Occasionally this ulceration progressed to a noma-like necrosis of the cheek. The lungs showed hemorrhage and edema at and above 700 r. The immature gonads appeared grossly normal but showed microscopically radiation damage at and above 400 r; this was more clearly recognizable in the ovaries than in the testes. Atrophy of the adrenal cortex was observed in animals dying later than 2 months; however, in animals dying 1 to 3 weeks after irradiation, the adrenals were often hypertrophic. The other organs showed no changes which could be attributed to a direct radiation effect. An interesting finding was that a high percentage of the monkeys which survived the acute radiation damage, died many weeks or months after irradiation of generalized tuberculosis. Since this was not observed in controls, it must be interpreted as lowering the resistance to infection by the total body irradiation.

Eighteen monkeys were used as controls for the irradiated groups. These monkeys were taken from the same shipments and were housed in the same quarters. Each of these control monkeys was inserted in the perforated polyethylene cage, transported to the radiology department, and positioned in the same arrangement and for the same time as the irradiated group. Thus, the controls went through exactly the same procedure as the irradiated animals, except that the roentgen-ray machine was not turned on. None of these monkeys died within 30 days or showed any unusual symptoms.

MORTALITY DATA

Table 1 shows mortality data of 110 irradiated monkeys. Actually, 116 monkeys were irradiated. For the analysis of the mortality, however, 6 deaths were excluded which in our opinion were not due to radiation effects. Two of these monkeys belonged to the 400 r group, the other 4 to the 300 r group. The 2 monkeys in the 400 r group were noted to be sick during the radiation and died at one and at six days.

TABLE I

MORTALITY OF MONKEYS AFTER SINGLE DOSE TOTAL BODY IRRADIATION

1	2	3	4	5
Dose Level	Number of Monkeys	Survivors at 30 Days	Survival Time in Days of Animals Dying within 30 Days	
			Average	Range
300 r	23	22 = 96%	18.0	18–18
400 r	9	7 = 77%	15.5	10–21
500 r	25	15 = 60%	17.0	11–29
600 r	9	4 = 44%	13.8	9–17
700 r	26	2 = 8%	12.1	6–23
800 r	9	0 = 0%	8.2	6–12
900 r	9	0 = 0%	8.1	6–10
	110			

The earliest death observed in other 400 r monkeys occurred at ten days. Of the 4 monkeys in the 300 r group, 1 died one day after irradiation, probably from injuries received after escape and recapture after the irradiation. The 3 other monkeys of the 300 r group died at six days. They belonged to a shipment of 12 sick monkeys. The nonirradiated 9 monkeys of this group also died at the same time or within three days. The earliest death observed in other 300 r monkeys occurred at 18 days. It is, of course, unfortunate to make such exclusions, but the experience of our group in handling monkeys and in recognizing sick monkeys was limited in the beginning.

Column 4 shows the average survival time of the animals which died within 30 days after the irradiation. These figures as well as the survival range in Column 5 also show a pronounced dependence on the dose in good agreement with the findings of Eldred and Trowbridge.[2]

Figure 5 shows the mortality curves of the various groups up to 100 days. It is apparent that due to the greater number of animals used for the groups at 300 r, 500 r

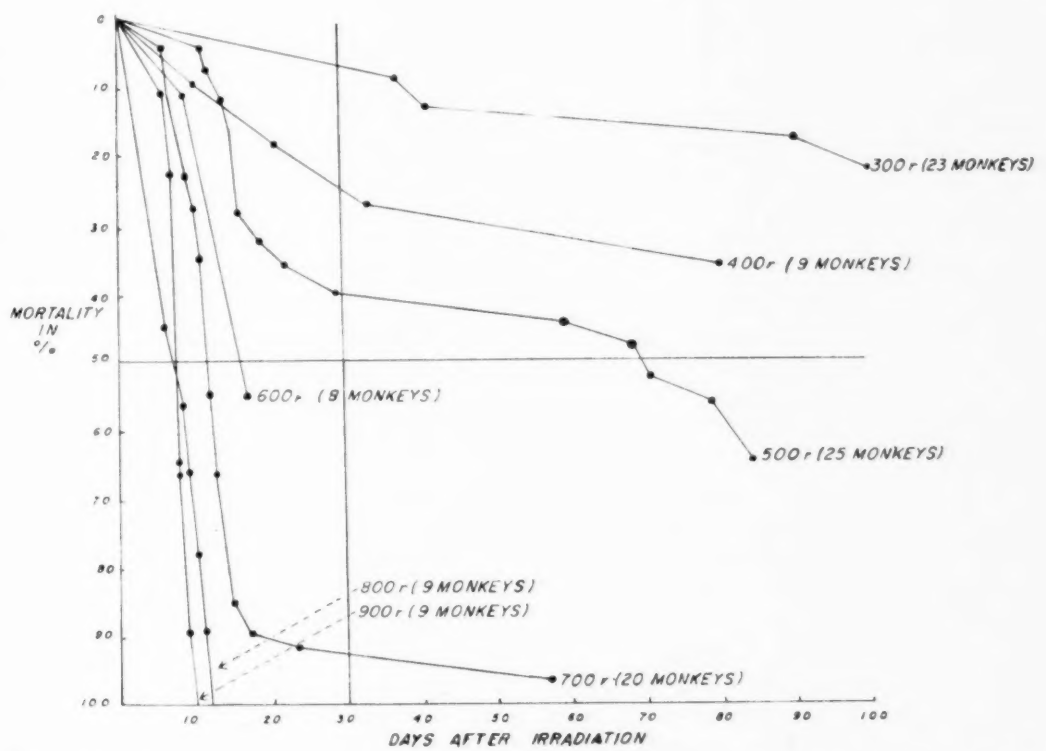

FIG. 5. Mortality of 100 rhesus monkeys after various doses of single exposure total body irradiation.

and 700 r the curves are more regular, while the fluctuations due to the small number are evident in the other curves.

For the determination of the LD 50/30 the values for the mortality at 30 days were subjected to a statistical analysis. A probit analysis was used following a suggestion of Dr. Brandt, biometrician of the New York Operations Office of the Atomic Energy Commission. The procedure is outlined in the "Statistical Tables" by Fisher and Yates. The calculations were carried out by Mr. Robert Silverman, assistant instructor in the Department of Mathematics of the Ohio State University. A separate report on these statistical calculations is available upon request. Essentially, the method amounts to finding the straight line which best fits the mortality values if these are plotted on probability graph paper. From many other studies, it is known that typical mortality curves for higher animals are straight lines in this form of presentation.

Figure 6 shows the most probable straight line arrived at by the statistical calculations. The points at 300 r, 500 r and 700 r, all of which were determined with at least 23 monkeys, lie close to this line. The 400 r and 600 r values, which were determined with only 9 animals, lie farther away. The line crosses the 50 per cent mortality level at 530 r and this value is therefore taken as the LD 50/30 day dose. The standard deviation was calculated to be ± 21 r.

Figure 7 shows the same curve and the same values as Figure 6, but in linear coordinates. The curve shows the typical "S" form.

COMPARISON WITH STUDIES IN MICE

It is interesting to compare our studies on monkeys with the studies on smaller laboratory animals, in which a great number can be used, in which uniform animals can be selected, and in which many other conditions can be more rigidly controlled. The most careful studies in this respect have been carried out over a period of many

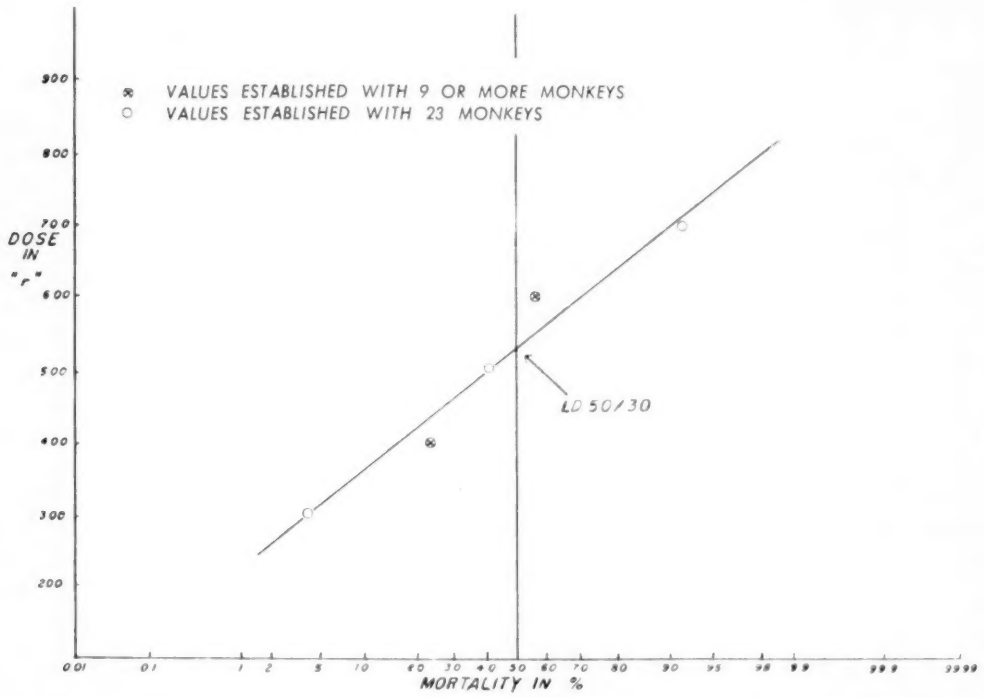

FIG. 6. Mortality of rhesus monkeys at 30 days after single exposure total body irradiation on probability scale.

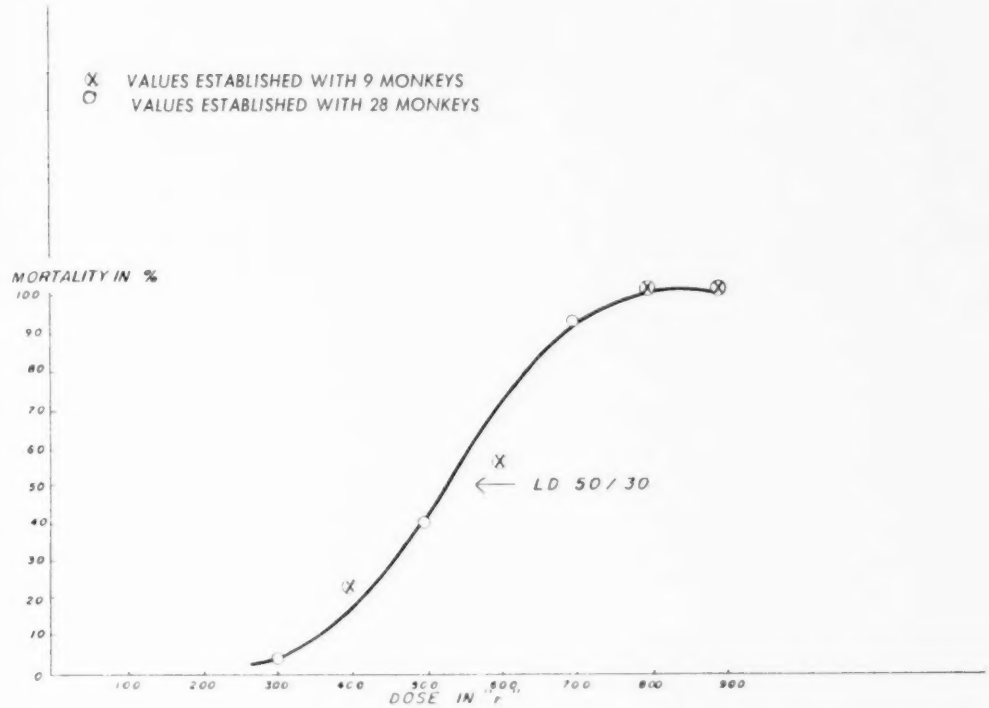

FIG. 7. Mortality of rhesus monkeys at 30 days after single exposure total body irradiation on linear scale.

years by Ellinger and his associates at the National Naval Medical Center in Bethesda, Maryland. Ellinger determines his doses in a way which is known in radiation therapy as "air doses", while in this publication and in most other reports the doses are determined in a way which is known in radiation therapy as "tissue doses." "Tissue doses" are equal to "air doses" plus backscatter. Ellinger has carefully determined the amount of the backscatter in his set-up to be 37 per cent. It is therefore easily possible to calculate from Ellinger's values the "tissue doses" by adding 37 per cent to the "air doses." The resulting values are plotted in Figure 8 on the same probability paper and in the same scale as our monkey values in Figure 6. It so happens that the LD 50/30 of Ellinger's mice is 530 r and thus coincides with the LD 50/30 of our monkeys. Although more than 100 mice were used for most of Ellinger's values, there is about as much scattering around the straight line as for our monkey values. This unexpected good agreement of the monkey mortality data was taken as an indication for satisfactory fulfillment of the problem assigned to us. It was felt that the accuracy of the LD 50/30 value would not be increased significantly by further experiments at 400 r and 600 r. These were originally scheduled to determine the 400 r and 600 r points with the same number of animals as the 300 r, 500 r and 700 r points.

In Figure 9, the average curves of the present monkey study are compared with Ellinger's mice experiments. The two curves cross at the LD 50/30 point; however, the monkey curve is distinctly steeper. This is of interest from practical and theoretical viewpoints. The steepness of the mortality curve also suggests that procedures designed to decrease the mortality after total body irradiation may be more effective in the rhesus monkey and perhaps also in man than in the mouse.

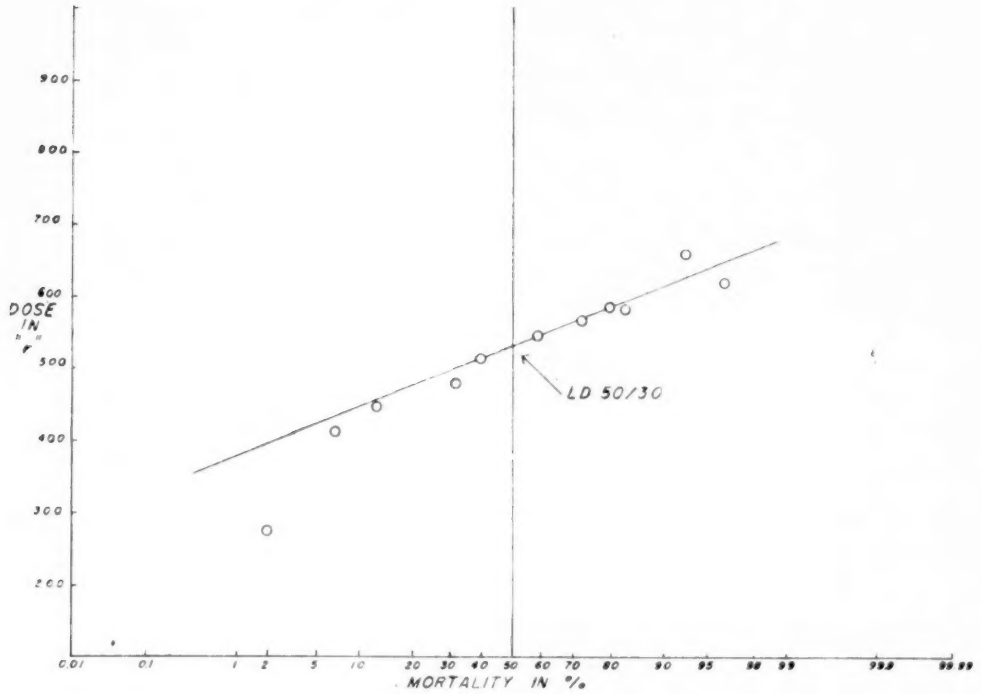

FIG. 8. Ellinger's values for mortality of mice (with 37 per cent backscatter added to his air doses) at 30 days after single exposure total body irradiation.

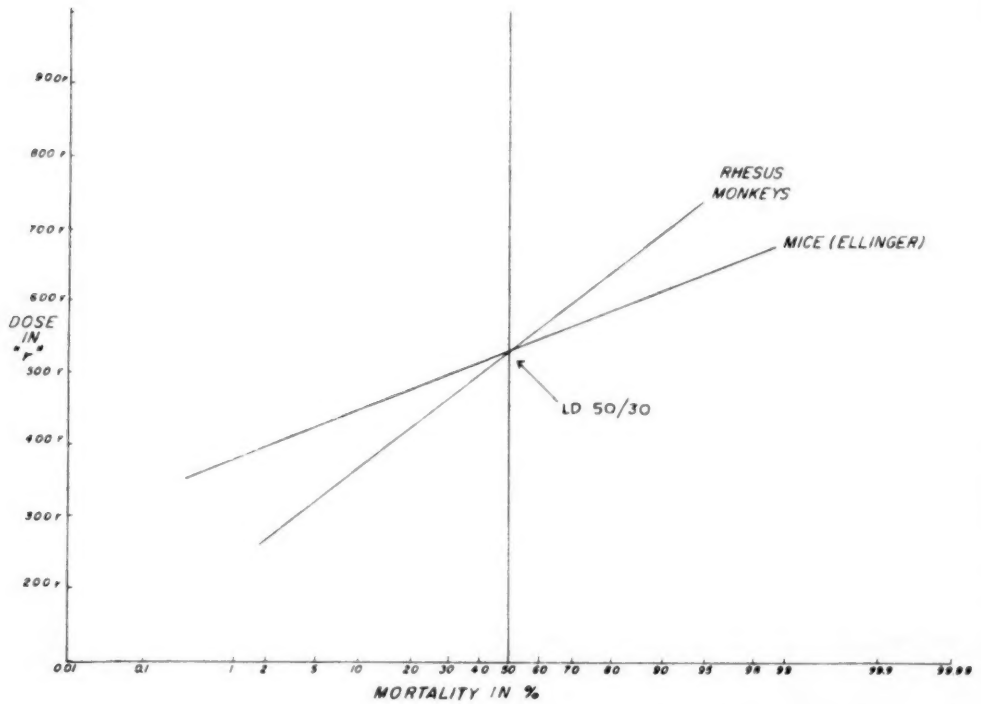

FIG. 9. Comparison of the slopes of the 30 day mortality curves for monkeys and mice.

SUMMARY

The mortality of rhesus monkeys after a single dose of total body irradiation was determined with a rotational arrangement using roentgen rays of 250 kv. and a half-value layer of 1.7 mm. copper. The LD 50/30 was found to be 530 r ± 21 r. The rhesus monkey mortality curve has a steeper slope than the mouse mortality curve.

U. K. Henschke, M.D., Ph. D.
Memorial Center
444 East 68th Street
New York 21, New York

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MAXIMUM PERMISSIBLE RADIATION EXPOSURES TO MAN

A PRELIMINARY STATEMENT OF THE NATIONAL COMMITTEE ON RADIATION PROTECTION AND MEASUREMENT

INTRODUCTION

SINCE the publication of NBS Handbook 59 on Permissible Dose from External Sources of Ionizing Radiation, the National Committee on Radiation Protection and Measurement (NCRP) has continued the study and review of its recommendations, particularly with respect to genetic effects and the possible shortening of average life expectancy due to radiation exposure of a larger fraction of the population. The NCRP proposals resulting from these studies had an important influence on the decisions reached by the International Commission on Radiological Protection (ICRP) in Geneva in April, 1956, which resulted in a general lowering of the maximum permissible accumulated dose (MPD) for occupational radiation exposures, as well as for exposures of the population as a whole. These changes are in accord with the informal agreements reached by the ICRP in Stockholm in 1952.

The NCRP has now agreed upon the formulation of revised recommendations on maximum permissible doses which integrate the national and international views for practical application. The Committee is pleased to note that the findings of the ICRP are reinforced by the important information and data provided in the subsequent reports of the National Academy of Sciences and the British Medical Research Council.

The changes in the accumulated MPD are not the results of positive evidence of damage due to use of the earlier permissible dose levels, but rather are based on the desire to bring the MPD into accord with the trends of scientific opinion; it is recognized that there are still many uncertainties in the available data and information. Consideration has also been given to the probability of a large future increase in radiation uses. In spite of the trends, it is believed that the risk involved in delaying the activation of these recommendations is very small if not negligible. Conditions in existing installations should be modified to meet the new recommendations as soon as practicable, and the new MPD limits should be used in the design and planning of future apparatus and installations. Because of the impact of these changes and the time required to modify existing equipment and installations, it is recommended on the basis of present knowledge that a conversion period of not more than five years be adopted within which time all necessary modifications should be completed.

DEFINITIONS

For the purposes of this preliminary statement, the following tentative definitions are given:

Controlled Area. A defined area in which the occupational exposure of personnel to radiation or to radioactive material is under the supervision of a radiation safety officer. (This implies that a controlled area is one that requires control of access, occupancy, and working conditions for radiation protection purposes.)

Workload. The output of a radiation machine or a radioactive source integrated over a suitable time and expressed in appropriate units.

Occupancy Factor. The factor by which the workload should be multiplied to correct for the degree or type of occupancy of the area in question.

RBE Dose. RBE stands for relative biological effectiveness. An RBE dose is the dose measured in rems. (This is discussed in the forthcoming report of the International Commission on Radiological Units and Measurement.)

MPD RECOMMENDATIONS FOR OCCUPATIONAL CONDITIONS (CONTROLLED AREAS)

1. *Accumulated Dose.* The maximum permissible accumulated dose, in rems, at any age, is equal to 5 times the number of years beyond age 18, provided no annual increment exceeds 15 rems. Thus the accumulated MPD = 5 (N − 18) rems where N is the age and greater than 18. This applies to all critical organs except the skin, for which the value is double.

2. *Weekly Dose.* The previous permissible weekly whole-body dose of 0.3 rem, and the 13 week dose of 3 rems when the weekly limit is exceeded, are still considered to be the weekly MPD with the above restriction for accumulated dose.

3. *Emergency Dose.* An accidental or emergency dose of 25 rems to the whole body, occurring only once in the lifetime of the person, shall be assumed to have no effect on the radiation tolerance status of that person. (See National Bureau of Standards Handbook 59.)

4. *Medical Dose.* Radiation exposures resulting from necessary medical and dental procedures shall be assumed to have no effect on the radiation tolerance status of the person concerned.

MPD RECOMMENDATIONS FOR THE WHOLE POPULATION

5. The maximum permissible dose to the gonads for the population of the United States as a whole from all sources of radiation, including medical and other man-made sources, and background, shall not exceed 14 million rems per million of population over the period from conception up to age 30, and one-third that amount in each decade thereafter. Averaging should be done for the population group in which cross-breeding may be expected.

RECOMMENDATIONS FOR INTERNAL EMITTERS

6. In controlled areas, the permissible radiation levels for internal emitters will conform to the general principles outlined above. Where the critical organ is the gonad or the whole body, the maximum permissible concentrations of radionuclides in air and water will be one-third the values heretofore specified for radiation workers. Where single organs other than the gonads are regarded as the critical organ, the present maximum permissible concentrations will continue. For individuals outside of controlled areas, the maximum permissible concentrations should be one-tenth of those for occupational exposures. (Other changes in the maximum permissible concentrations for radionuclides may be introduced because of additional information developed since the publication of National Bureau of Standards Handbook 52.)

DISCUSSION OF REVISED RECOMMENDATIONS

7. The MPD for occupational exposure is based on the absence of detectable injury to the individual. It remains at its present level of 0.3 rem/week for the whole body. Where the dose in any week exceeds this value, a dose of 3 rems in 13 weeks may be accepted. The 13-week period may start at the beginning of the calendar quarter or the beginning of the week during which the permissible weekly dose was exceeded.

8. The rules given in Handbook 59 will be continued for operational and administrative purposes, but some of the rules will be modified by provisions related to an average yearly limitation of occupational exposure to external sources of ionizing radiation of 5 rems to the blood-forming organs, gonads, and lens of the eyes, and of 10 rems to the skin. The use of "5 rems" in the statement of the revised rules is for the purpose of design and administration. The critical limitation will be that defined for the total accumulated dose in paragraph 1 above.

9. If a person's occupational exposure is documented or otherwise known with reasonable certainty, he may be permitted to use his reserve exposure in accordance with paragraphs 1 and 2 above. In all other cases, he shall be assumed to have received

his maximum accumulated dose as indicated in paragraph 1 above.

10. It is considered that with the current and proposed low levels of occupational exposure, it is presently not necessary to make special allowance for medical exposure in conjunction with occupational exposure. This consideration may later become important. The effects of medical exposures have long been considered by this Committee to be the responsibility of the attending physician; it is his responsibility to evaluate medical radiation exposure in relation to the health of the individual. (See National Bureau of Standards Handbook 59.)

11. In the determination of the population dose in the vicinity of radiation sources proper consideration should be given to occupancy factor and to workload. The exposure of individuals outside of controlled areas may be integrated over periods up to one year.

12. While at the moment it is not feasible to determine the average exposure for the population with any reasonable accuracy, the adoption of some figure is necessary for planning purposes. For the immediate future, it may be assumed that the total integrated RBE dose received by all radiation workers will be small in comparison with the integrated RBE dose of the whole population. Furthermore, persons outside of controlled areas, but exposed to radiation from a controlled area, constitute only a small portion of the whole population. Therefore, if this small portion is assumed to receive yearly an average per capita dose of 0.5 rem, the total dose to the whole population from man-made radiations is not likely to exceed 10 million rems per million of population up to age 30. (This assumes a dose of 4 million rems per million population over this age period from background radiation.)

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EDITORIALS

THE PHILOSOPHY UNDERLYING RADIATION PROTECTION*

IN THE broad sense, radiation protection is a problem that will touch the lives of most of us more and more as time goes on, whether it be in connection with nondestructive testing, with radiology, or with the production of nuclear power. The uses of radiation-producing machines and the use of radioactive materials will undoubtedly increase as time goes on, and radiation, as such, will become an increasingly important part of our national economy.

The substance of this discussion has to do with the development of our philosophy of radiation protection and the development of radiation protection standards.

The term "radiation-protection standards" is used somewhat loosely and yet at the same time there is probably very little real uncertainty as to the broad meaning of the term. One normally thinks of a standard as being something rather firm, rather well understood, inflexible, accurately known, and reproducible. When a standard is mentioned, one immediately thinks of something like the standard meter-bar, carefully locked away in a vault and resistant to the changes of time; or of some accurately measurable quantity, such as the ohm or volt.

However, in the field of radiation protection standards, there are many unknowns and many uncertainties. They involve a great many assumptions that may have to be changed from time to time. In fact it would not be over-simplifying the case to state that our protection standards are essentially protection goals or objectives. Where it is possible to develop numbers to assign to some of the standards, these numbers are really more in the nature of a means to achieve some goal than the goal itself. Even the goal itself is difficult of definition. It is primarily to determine the limits of radiation exposure to which the individual, or whole population, can be exposed without encountering risks incommensurate with the benefits to be expected from its use. Standards of safety go back directly to the individual who will be exposed to radiation. For this it is necessary to determine how much radiation he can absorb without injury to himself or to his progeny.

If one considers the complication of the human being as an organic structure, and the great difference in sensitivity between individuals, it is very easy to see why such a determination becomes an extremely difficult problem. To point up the difficulties, it may be helpful to review briefly some of the early background and philosophy leading to the development of standards of radiation protection.

Radiation was recognized as a potential hazard to health soon after its discovery. Efforts to understand and curtail radiation exposure to individuals, however, were not begun seriously until the 1920's. One should bear in mind that it was not until 1928 that the world had a uniform and acceptable unit of radiation dose, namely the roentgen. Consequently, radiation-protection efforts and protection standards were, of necessity, on a purely qualitative basis. Until 1928, most radiation treatments were expressed in terms of fractions of an erythema dose—the amount of radiation that would cause a defined reddening of the

* Abridged from an Address presented to the Ninth Annual Conference on Electrical Techniques in Medicine and Biology, November 7, 1956, New York, New York.

skin. This in itself was a very uncertain factor, since it depended upon the energy of the radiation, the time over which it was delivered, the size of the irradiated field, and the amount of backscattering, not to mention the individual's idiosyncrasy with regard to radiation sensitivity. It was not until the mid-30's that stray radiation exposure was measured quantitatively, thus making it possible to put radiation-protection standards on a reasonably firm quantitative basis. Interestingly enough, later efforts proved that these early standards were not grossly wrong.

One could venture the suggestion that if there is any basic standard of radiation protection it would be what is now referred to as the maximum permissible dose, or maximum permissible exposure of an individual. By maximum permissible exposure is meant the amount of radiation to which the whole body of an individual can be subjected over the period of his adult lifetime, without producing in that individual any detectable harmful effects. For the occupational exposure of an individual to radiation, such a standard might be adequate, but another basic standard is needed for the exposure of the entire population—one that takes the genetic effects into consideration.

Parenthetically, it should be remarked that the old term "tolerance dose" that prevailed for many years is a complete misnomer. There is no such thing as a "tolerable dose of radiation." No radiation, other than for the treatment of disease, is known to be beneficial to man. Any radiation exposure received by man must be accepted as harmful. Therefore, the *objective should be to keep man's exposure as low as possible and yet, at the same time, not discontinue the use of radiation altogether.*

The big problem is to obtain some quantitative idea as to the degree of harm that will result from exposure to various amounts of radiation.

As mentioned above, early permissible exposures were expressed in terms of the erythema. This followed as a result of a very few observations made on a very few people who had been overexposed to radiation under conditions where there was some crude idea as to the amount of radiation involved. As a result of this, numerous proposals were made and for a time served a useful purpose. For example, Mutscheller proposed as a "tolerance dose," 1/100 of an erythema dose in 30 days. Others reduced this to 1/1000 of an erythema dose in 3 days. Sievert independently proposed 1/10 of an erythema dose per year.

In retrospect, these standards look pathetic indeed, and yet they marked important milestones leading to our more accurate understanding of the problem. When one realizes that, on the basis of today's knowledge, an erythema dose under given conditions may vary from 270 to 1,000 roentgens over a range of 100 to 1,000 kilovolts, some visualization of the vast uncertainties in the early work might be had.

By the early 30's such standards were correlated and reconciled by the free use of "safety factors." Germany proposed the first quantitative expression of a permissible dose measured in roentgens, arriving at a figure of 10^{-5} roentgen per second as their so-called tolerance level of radiation. In 1934 it was possible, for the first time, for the International Commission on Radiological Protection to express permissible exposure in terms of roentgens. The value then chosen was 2/10 roentgen per day. In the United States in 1936 a somewhat lower level, namely 1/10 roentgen per day was adopted. This lower value was in part a result of the belief that there was not an adequate safety factor in the international recommendations.

It will be noted that the permissible exposures mentioned above were integrated over varying lengths of time, ranging over a period of one second to one year. Although precise information on radiation recovery is lacking, it is undoubtedly true that a given dose of several roentgens received in a period of a few minutes is probably more harmful to the individual than

the same dose distributed evenly over a year's period of time. Therefore, while the various proposals for permissible exposure appear to reduce numerically to the same quantity, they were not, in fact, biologically equivalent.

In 1946 the National Committee on Radiation Protection (NCRP) undertook an intensive review of the whole problem of permissible dose. This review was instigated by the fact that, during the Manhattan District days, a tremendous amount of experimental and biological research had been carried out for the purpose of assuring safety to radiation workers; new biological data had become available. It was quickly realized that the value 1/10 roentgen per day, as used in this country, provided only marginal protection. There was increasing evidence leading the committee to believe that the value should be lowered. At the same time, it was decided to review the question of the period over which the dose would be integrated. For technical, as well as administrative reasons, it appeared that integration over one day was unnecessarily restrictive. Integration over about one month appeared to be more reasonable and a compromise was finally reached at one week. The committee arrived at the recommendation of 3/10 roentgen per week as the permissible whole-body exposure to gamma rays and to moderate and medium energy roentgen rays. This value was later adopted internationally.

There is one very important fact that should be emphasized at this point. From 1928 to 1936, the permissible exposure was 1/10 of an erythema dose or 50 to 100 r per year; from 1936 to 1948 it was 36 r per year; since 1948 it has been 15 r per year. Now as far as is known, there is not a single case on record where an individual who has maintained his exposure within any of these limits, has developed any detectable injury that can be reasonably ascribed to that radiation exposure. One may ask with some reason, why, with such an imposing negative record, has there been a steady lowering of the permissible exposures, and why still further reductions are being considered. The reason for the 1948 change has been well documented in the NCRP report on the permissible dose from external sources of ionizing radiation. This was published as NBS Handbook No. 59, *Permissible Dose from External Sources of Ionizing Radiation.*

Thus far in this discussion, the problem of radiation exposure to the individual has been considered only under essentially occupational conditions. There are a number of other conditions that have to be considered. Radiation effects on human beings may be more or less significant depending upon many factors. For example, there is increasing evidence that irreversible genetic damage may result from exposure of the gonads to any amount of radiation. All such exposure is cumulative. This implies that an exposure that may not produce any harm to the individual himself may be passed down through the genetic chain to the descendants of this individual. One cannot neglect the possibility that such damage may occur.

It should be pointed out that the importance of this problem has been evident to the National Committee and the International Commission for at least the past 10 years. The problem was clearly recognized by the NCRP in 1946 when it established a new subcommittee on permissible radiation exposure and included 3 geneticists in its membership. In its final report, issued as NBS Handbook 59, there was frequent mention of the problem although it was felt then that there was insufficient evidence to warrant the establishment of further quantitative limitations on exposure for purely genetic reasons.

In addition to genetic considerations, attention was given to the possible effect of radiation exposure upon the average expected life span. Here again, on the basis of animal experiments as well as some limited human data, there was some evidence that either chronic or acute exposure of the whole body to radiation might statistically shorten one's life expectancy. For partial

body exposure the effect would be only a fraction of that for whole-body exposure. When Handbook 59 was released, quantitative information on these questions was meager; more has recently been provided by the report on *The Biological Effects of Atomic Radiation* by the National Academy of Sciences.

These facts, if facts they be, are not such that much comfort can be derived from them. But, they should be considered in proper perspective and in relation to the many other complicated facets that may influence our lives in much the same way.

The National Committee on Radiation Protection felt it essential to minimize these additional and, to some degree, controllable risks that may be associated with the use of radiation. To this end, it is now proposing a general lowering of the maximum permissible exposure levels for both radiation workers and for the general population. These changes are patterned after the 1956 recommendations of the ICRP, and are presented in preliminary form in the notice issued by the NCRP which is published elsewhere in this issue of the JOURNAL.

At this point let us think a little about what we have done. Of course it is clear that over a period of many years we have set physical limits to the radiation exposure that man may be allowed to accept. It is also clear that there is an almost total lack of direct experience on the effects of radiation on man. There is a wealth of indirect experience.

Also—and this is a most impressive fact—there are virtually no cases where persons subjected to any of the permissible exposures of radiation have evidenced any detectable harm to *themselves*.

Let us pause a moment to consider this most unusual situation which has almost no parallel in industrial hygiene. In the well-known situation with silicosis, there was clear evidence as to cause and effect, and positive steps could be taken to minimize its incidence. Similar to radiation, in a sense, is the fact that the disease might first show itself many years after the exposure to silica dust occurred. However—and differing from radiation—once the disease has developed there is a positive relationship to its cause; this is the case with most industrial toxic agents.

One of the most important—if not the most important—aspects of radiation injury is the absence of a clear and definable relationship between the exposure and the end result. Many of the manifestations of disease that can be ascribed to radiation exposure can equally well develop in persons who have absolutely no radiation exposure history. Considering this, together with the fact that radiation exposure does not excite any of our ordinary sensory organs, makes it loom as a hazard quite distinct from all others. It is primarily for these reasons that such an enormous effort has been expended over the past 30 years on matters of radiation protection. It is surely why, with this particular hazard, we are today relatively so much further ahead than we might be with any other hazard having such a short history. It is the reason why we are doing so much to prevent something from ever happening.

There are perhaps other reasons which exist even though we may not ordinarily think of them as such.

I am reminded of an incident that occurred at a scientific meeting a few years ago. In the course of the discussion of a paper on radiation protection, I was taken to task for having used the phrase, "the science and philosophy of radiation protection." The discussant insisted that the radiation protection problem was straightforward, scientific and clean-cut and that there was no argument as to permissible exposure levels and such. I can think of nothing further from the truth.

The basic problem is even more complicated than just science and philosophy.

Today, as we consider the total problem of radiation exposure, it is certain that we are forced to consider not only the philosophical and scientific aspects but also the aspects of morality. There is no line as to where one begins or the other ends.

Consider the most beneficial use of radiation that we can think of—the diagnosis and treatment of disease. No one can question the enormously important benefits that radiation offers in improving our health. To deny ourselves this tool is to take a step back toward the dark ages. Yet, as we now know, it carries some element of risk—not necessarily to ourselves but to some unknown, unborn person at some unknown time in the future. How can we balance the choice between our own health—or possibly even our own survival—between this and that unidentifiable life of the future. I suspect the answer is clear, but can we be sure?

For the present, we must preserve our sense of proportion. Through misunderstanding and many confusing public statements, the public does not know what to do. This is becoming more evident daily, as we hear of people refusing to have chest roentgenography or dental examinations. There is no future for that unborn child if first we die of tuberculosis or infection. Here is where our sense of proportion enters.

For the radiologist or physician or dentist, it is essential that he know more about matters of protection. It is essential that he be trained to perform the necessary examination with the very minimum of exposure to the patient. It is essential that he have equipment designed to minimize or eliminate exposure that serves no useful purpose. It is essential that he know the dose that he administers—at least within some reasonable limits. If he knows this he will almost surely become aware of the protection problem.

For the individual—the prospective patient—it is essential that he place confidence in the physician. The ordinary individual cannot exercise judgment as to the need for radiation diagnosis any more than he can as to the usefulness of a particular prescription. He can, however, avoid unnecessary radiation by not "shopping around for better X-rays," by not using such foolish things as "shoe-fitting X-ray machines," and by not bringing unnecessary radioactive devices into his home. Let him keep his sense of proportion.

Consider the genetic problem. Let us assume that the geneticist is correct in predicting that if we expose the population to an average per capita dose of X rem, we will produce Y genetic deaths at some time within the next Z generations where Z may be any number up to say 50. (This is of the order of 1,000 or 1,500 years.) Let us note that these deaths will be in such forms as failure to conceive, still-births, miscarriages, death below the average lifetime and so on. Let us also note that few if any of these deaths will ever be individually and causatively related to some specific earlier genetic damage caused by radiation. This lack of knowledge gives us no right to needlessly cause such damage. It has been demonstrated that some shortening of the average life expectancy may result from radiation exposure. There is no evidence that improved medical diagnosis made possible by the use of roentgen rays does not more than offset this.

On the other side of the ledger, let us note that through the use of radiation today we may be able to better our lives either as to material things or as to health. But even here—strange to say—the problem is complicated by our enormous improvement in health. Many who have faced the problem will question the wisdom of prolonging life to the point of so greatly increasing the number of people in the state of senility. Others will question the wisdom of prolonging, in misery, the lives of those unfortunates for whom there is no hope in living. The answers to these problems are largely matters of ethics and morality. Of course, it must be admitted that through overexposure to radiation we may well augment rather than decrease these numbers.

In any case, with all our knowledge today, we are still dealing with a large number of imponderables. Are we to be morally charged with murder if through our judgment today we allow—or cause—these

genetic deaths of the future? Can we leave to the future generations the problem of somehow adjusting themselves to an environment of higher radiation levels? Will the future race be better off or worse off with whatever changes may take place in it? The answer here may lie in whether or not this future race, having knowledge of itself, will consider that it has reached perfection—as apparently we now consider ourselves to have done. This is a matter of opinion.

We pride ourselves today on our greatly increased stature developed over the past few hundred years. For what purposes? It just necessitates a bigger foxhole to keep from being shot by the other guy. A genetic improvement? I sometimes think—facetiously, I'll admit—that we may be in more genetic danger today from automobiles and comic books than from radiation.

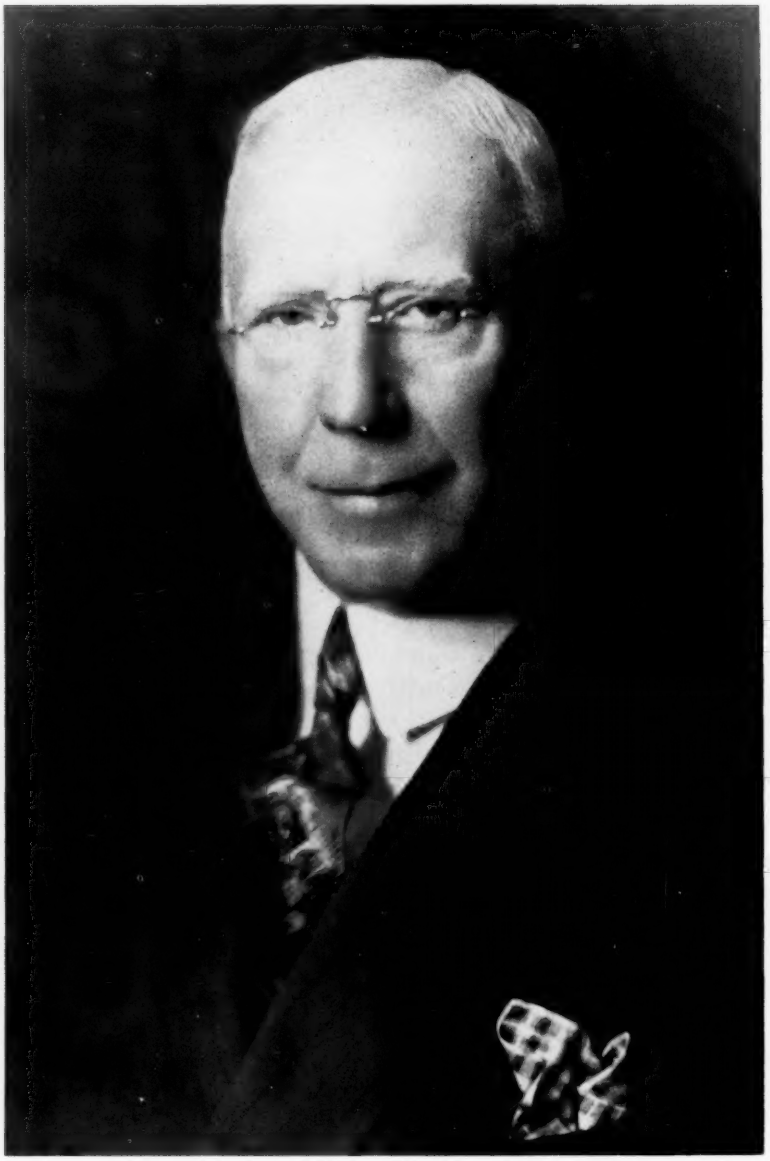
But putting all of these diversions aside I think our course today is relatively clear.

We must minimize our exposure to radiation. We must maximize the benefits it offers to our health and our material well-being. These two aims are mutually contradictory as far as we know today. Radiation protection is not only a matter for science. It is a problem of philosophy, and morality, and the utmost wisdom.

Lauriston S. Taylor

Atomic and Radiation Physics Division
National Bureau of Standards

We regret to announce the death on March 12, 1957, of Dr. Douglas J. Roberts, President-Elect of the American Radium Society.



GEORGE E. PFAHLER

1874–1957

DR. GEORGE E. PFAHLER was educated in an ungraded country school. He began his career as a school teacher. He graduated from the Bloomsburg Normal School, now State Teacher's College, Bloomsburg, Pennsylvania. His medical education was at the Medico-Chirurgical College of Philadelphia, subsequently amalgamated with the University of Pennsylvania. He was a Resident and an Assistant Chief Resident Physician in the Philadelphia General Hospital. He was the

Director of the Radiological Department of the Philadelphia General Hospital from 1899 to 1903.

In 1909 he was made clinical Professor of Radiology at the Medico-Chirurgical College and Hospital (the first recognition of this kind given to any American College), and two years later was made full Professor of Radiology.

He was subsequently made Vice-Dean of Radiology in the Graduate School of Medicine in the University of Pennsylvania. He had been Director of the Radiological Departments of the Graduate Hospital and Misericordia Hospital for many years.

His honorary degrees in this country and abroad are too numerous to enumerate. Ursinus College honored Dr. Pfahler by dedicating a beautiful new building in 1942 as the Pfahler Hall of Science, and then electing him as a member of the Board of Directors. They also conferred upon him honorary degrees of D.Sc. and LL.D.

He has served as Chairman of the Committee on Cancer Control at the Philadelphia County Medical Society for a period of 19 years, and was one of the Board of Directors and Honorary President of the Philadelphia Division of the American Cancer Society.

Dr. Pfahler served on the Executive Committee of the First and Second International Congresses of Radiology in 1925 and 1928 (held in London and Sweden). He was Honorary Vice-President of the Fifth International Congress of Radiology held in Chicago in 1937. He was Honorary Vice-President of the Sixth International Congress of Radiology held in London, 1950, and was named Vice-President Emeritus of the Seventh International Congress of Radiology held at Copenhagen in 1953 and of the Eighth International Congress of Radiology held in Mexico City in 1956.

Dr. Pfahler had served as President of both the American Roentgen Ray Society and the American Radium Society, and he treasured the great distinction of having been the First President of the American College of Radiology, 1922–1923. He was an Honorary Member of practically every radiological society of North America, South America and Europe. He had received six Gold Medals for outstanding achievement in the field of Radiology:

Strittmatter Gold Medal of the Philadelphia County Medical Society, American Roentgen Ray Society, American Radium Society, Radiological Society of North America, American College of Radiology, and First Medal Award from the Antoine Béclère Center of Paris. This last medal bore the inscription: "Thus paying homage to the Pioneer, who, more than fifty years ago—lightened the field of Radiology."

Dr. Pfahler was also granted the Award of Merit from the American Cancer Society and the Alumni of the Medico-Chirurgical College. The "Lehrbuch der Röntgen Diagnostik," by H. R. Schinz, W. Baensch, and E. Friedl, was dedicated to the Pioneers of Roentgenology and named Albers Schönberg, Germany; Antoine Béclère, France; Gösta Forssell, Sweden; Guido Holzknecht, Austria and George E. Pfahler, America.

Dr. Pfahler will ever be remembered as one of the great pioneer radiologists of America. His interest in therapy began soon after the discovery of roentgen rays. He was a vigorous champion of the possible advantages of irradiation in the treatment of cancer. He rarely missed a radiological meeting, presented many papers of his own, and could always be counted upon for an interesting and forceful discussion of other papers on the program.

An ardent traveler, Dr. Pfahler was also a marvelous photographer. His interesting travelogues embraced many sections of interest and beauty in North and South America, Canada and Europe. Before color photography was developed, he spent hours tinting with water color many photographs of his vacation travels.

Dr. Pfahler worked up to the day before his death, January 29, which was his eighty-third birthday.

The last honor conferred upon him was by the members of the Blockley Radio-

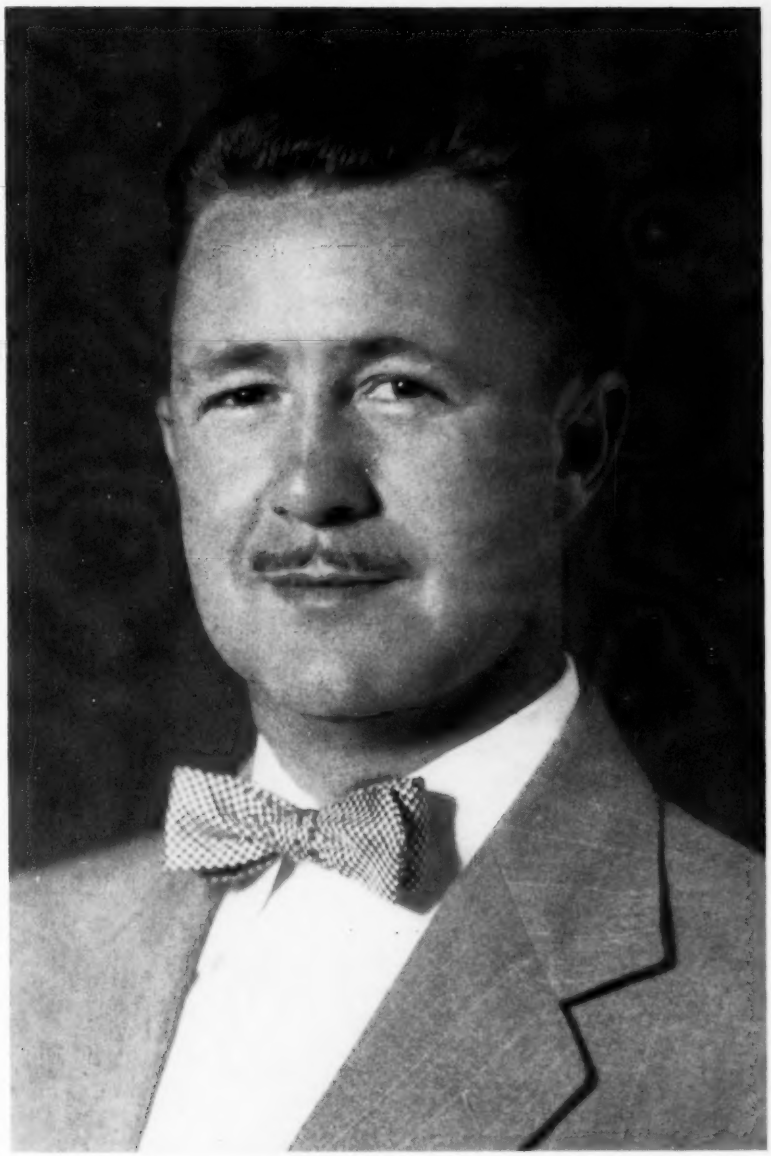
logical Society (Ex-Residents of the Philadelphia General Hospital). This was a particularly fitting recognition because Dr. Pfahler was, from 1899–1903, the first radiologist at the Philadelphia General Hospital, one of the finest and largest teaching centers in Philadelphia and America. It affords teaching services to five medical schools in Philadelphia and is traditionally known as the first hospital in the Philadelphia area.

The scroll presented to Dr. Pfahler at a meeting of the Blockley Radiological Society, Philadelphia, May 12, 1956 reads:

"The Blockley Radiological Society in recognition of his many years of devoted service to the advancement of radiology.—George E. Pfahler, M.D.

"Pioneer, radiologist, distinguished teacher, author, scientist, scholar and founder of the Department of Radiology of the Philadelphia General Hospital, has been duly elected honorary member."

B. P. Widmann, M.D.



CHARLES LUTHER HINKEL
1910–1956

RADIOLOGISTS lost an outstanding colleague on December 10, 1956 when Dr. Charles Luther Hinkel died suddenly of a coronary occlusion. Dr. Hinkel had just returned from a meeting of the Radiological Society of North America in Chicago, where he had read a paper on "Fractures and Dislocations of the Wrist."

Dr. Hinkel was a native of West Grove, Pennsylvania. He took his M.D. degree at the University of Pennsylvania in 1936 and interned at Geisinger Memorial Hos-

pital in Danville, Pennsylvania. He received his specialty training in radiology at Columbia-Presbyterian Medical Center, New York, from 1937 to 1940. During the two years he was on the staff of Presbyterian Hospital he received a Doctor of Medical Science degree from Columbia University. He served in the United States Army Medical Corps from 1942 to 1946, attaining the rank of Lieutenant Colonel. He played an important part in organizing the Army Radiological Services in England during World War II and was awarded the Bronze Star for his outstanding accomplishments. In 1946, Dr. Hinkel returned to the Geisinger Hospital and Foss Clinic as Director of the Department of Radiology, a position which he held at the time of his death. "Luke" Hinkel was a tireless research worker, having published thirty-three scientific papers on a wide variety of subjects during his sixteen year career. Two papers and a chapter in an orthopedic book were in press at the time of his death. He was particularly interested in gallbladder disease and had done extensive research on the formation and nature of gallstones.

Dr. Hinkel was a Councilor to the American College of Radiology and was Chairman of its Advisory Committee to the American Society of X-ray Technicians. In this capacity he spent much of his time in the development of schools for radiologic technicians and in the maintenance of their standards. In 1954, he developed an aptitude test for radiologic technicians which is now available throughout the United States. He was Chairman of the Exhibit Committee of the Pennsylvania Radiological Society, a member of the Radiological Society of North America, a member of the American Roentgen Ray Society, and an abstractor for the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE.

"Luke" was a great friend of those who knew him. His passing will be keenly felt by his colleagues, as well as by the numerous residents and technicians whom he trained. He is survived by his devoted wife and five children.

J. L. WILLIAMS, M.D.

SOCIETY PROCEEDINGS AND NEWS ITEMS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa. Annual meeting: Shoreham Hotel, Washington, D. C., Oct. 1–4, 1957.

American Radium Society
Secretary, Dr. Theodore R. Miller, New York, N. Y. Annual meeting: Chateau Frontenac, Quebec, Canada, May 30–June 1, 1957.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y. Annual meeting: To be announced.

American College of Radiology
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: To be announced.

Section on Radiology, American Medical Association
Secretary, Dr. T. Leucutia, Harper Hospital, Detroit 1, Mich. Annual Meeting, June 3–7, 1957, New York, N. Y.

Eighth International Congress of Radiology
Secretary General, Dr. José Noriega, Calle del Oro 15, Mexico 7, D. F.

Alabama Radiological Society
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

American Nuclear Society
Dr. L. D. P. King, Los Alamos Scientific Laboratory, Post Office Box 1663, Los Alamos, N.M.

Arizona Radiological Society
Secretary, Dr. R. Lee Foster, 1313 N. Second St., Phoenix, Ariz. Two regular meetings a year. The annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Dr. E. A. Mendelsohn, Holt-Krock Clinic, Fort Smith, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr. David M. Gould, University of Arkansas Medical Center, Little Rock, Ark. Annual meeting, May, 1957 at the University of Minnesota.

Atlanta Radiological Society
Secretary, Dr. Charles M. Silverstein, 3254 Peachtree St., N.E., Atlanta, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockly Radiological Society
Secretary, Dr. Samuel Finkelman.

Brooklyn Radiological Society
Secretary, Dr. Harold N. Schwinger, 62 8th Ave., Brooklyn, N. Y. Meets first Thursday of each month October through May.

Buffalo Radiological Society
Secretary, Dr. Charles Bernstein, 685 Delaware Ave., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse, N. Y. Meets January, May, November.

Central Ohio Radiological Society
Secretary, Dr. Arthur R. Cohen, 41 S. Grant Ave., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. Arthur S. J. Petersen, 11406 Parnell Ave., Chicago 28, Ill. Meets second Thursday of each month, October to April inclusive at the Sheraton Hotel.

Cleveland Radiological Society
Secretary, Dr. A. S. Tucker, 2065 Adelbert Rd., Cleveland 6, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

Colorado Radiological Society
Secretary, Dr. Lorenz R. Wurtzebach, 601 Nineteenth Ave., Denver, Colo. Meets third Friday of each month at Denver Athletic Club.

Connecticut Valley Radiologic Society
Secretary, Dr. T. J. Crowe, 53 Center St., Northampton, Mass. Meets second Friday October and April.

Dallas-Fort Worth Radiological Club
Secretary, Dr. A. H. Keene, 3707 Gaston Ave., Dallas, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Joseph O. Reed, Jr., Harper Hospital, Detroit, Mich. Meets monthly first Thursday, Oct. through May, at David Whitney House, 4421 Woodward Ave., at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Florida Radiological Society
Secretary, Dr. C. Robert DeArmas 135 Broadway, Daytona Beach, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

Georgia Radiological Society
Secretary, Dr. B. H. Malone, 1406 Reynolds St., Brunswick, Ga.

Greater Miami Radiological Society
Secretary, Dr. George P. Daurelle, Jackson Memorial Hospital, Miami, Fla. Meets monthly third Wednesday at 8 P.M. at Mercy Hospital, Miami, Fla.

Greater St. Louis Radiological Society
Secretary, Dr. Thomas F. Maher, 1015 Missouri Theater Bldg., St. Louis, Mo.

Houston Radiological Society
Secretary, Dr. John M. Phillips, 1203 Ross Sterling Ave., Houston 25, Texas. Meets fourth Monday each month, Meeting Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. Alfred M. Stone. St. Lukes Hospital, Boise, Idaho. Meets annually at same time as Idaho State Medical Association.

Illinois Radiological Society
Secretary, Dr. Stephen L. Casper, 1101 Maine St., Quincy, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. C. A. Stayton, 313 Hume-Mansur Bldg., Indianapolis 4. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. James T. McMillan, 1104 Bankers Trust Bldg., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

* Secretaries of societies are requested to send timely information promptly to the Editor.

Kansas Radiological Society
Secretary, Dr. A. M. Cherner, Hays, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. David Shapiro, 217 East Chestnut St., Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Ernest I. Melton, 2187 Ocean Ave., Brooklyn 19, N.Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Lewis J. Peha, 405 North Bedford Drive, Beverly Hills, Calif. Meets second Wednesday each month at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Irving L. Selvago, Jr., Maine Medical Center, 22 Arsenal St., Portland, Maine. Meets in June, September, December and March.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore, Md.

Memphis Roentgen Society
Secretary, Dr. James L. Booth, 899 Madison Ave., Memphis 4, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. H. D. Robertson, Miami Valley Hospital, Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. J. W. Walton, Horton Memorial Hospital, Middletown, N. Y. Meets 8:30 P.M., fourth Tuesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. R. W. Bryne, 3321 N. Maryland Ave., Milwaukee 1, Wis. Meets monthly on fourth Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. O. J. Baggenstoss, 1953 Medical Arts Bldg., Minneapolis, Minn. Meets three times annually, once at time of State Med. Assn., and in spring and fall.

Mississippi Radiological Society
Secretary, Dr. Robert P. Henderson, 316 Medical Arts Bldg., Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. John Stewart, 1105 Frederick Lane, Billings, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Jerome Zwanger, 126 Hicksville Rd., Massapequa, L. I., N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. J. F. Kelly, Jr., 816 Medical Arts Bldg., Omaha, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Raymond A. Dillon, 24 Wedgemere Ave., Winchester, Mass. Meets third Friday of each month, October through May, at Hotel Commander, Cambridge, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. John A. Evans, 525 East 68th St., New York 21, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. William H. Sprunt, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. Marianne Wallis, St. Joseph's Hospital, Minot, N. D. Meetings by announcement.

North Florida Radiological Society
Secretary, Dr. Marvin Harlan Johnston, Five Points Medical Center, Jacksonville, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Irving Van Woert, Jr., Albany Hospital, Albany, N. Y. Meets in Albany area on second Wednesdays of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. H. B. Stewart, 2920 Capital Ave., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. John R. Hannan, 10515 Carnegie Ave., Cleveland 6, Ohio. Annual meeting, Dayton, May, 1957.

Oklahoma State Radiological Society
Secretary, Dr. Sol Wilner, St. John's Hospital, Tulsa, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. N. L. Bline, 210 Jackson Tower, Portland 5, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. J. R. Raines, 214 Medical-Dental Bldg., Portland 5, Oregon. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Walter P. Bitner, 234 State Street, Harrisburg, Pa.

Philadelphia Roentgen Ray Society
Secretary, Dr. Roderick L. Tondreau, 3400 Spruce St., Philadelphia, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. N. B. Tannehill, 601 Jenkins Bldg., Pittsburgh 22, Pa. Meets second Wednesday of month, October through June at Hotel Roosevelt.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Paul W. Roman, 1810 Eutaw Place, Baltimore 17, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of Greater Cincinnati
Secretary, Dr. Morris M. Garrett, 630 Scott St., Covington, Ky. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Richard D. Moore, St. Francis Hospital, Honolulu 17, T. H. Meets third Monday evening of each month at designated hospitals.

Radiological Society of Greater Kansas City
Secretary, Dr. E. H. Stratemeier, Jr., 1010 Rialto Building, Kansas City 6, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. W. S. Neal, 602 Pere Marquette Bldg., New Orleans, La. Meets annually during Louisiana State Medical Society Meeting.

Radiological Society of New Jersey
Secretary, Dr. G. G. Green, 601 Grand Ave., Asbury Park, N. J. Meets at Atlantic City at time of State Medical Society and in November in Newark, N. J.

Radiological Society of Southern California
Secretary, Dr. Robert B. Engle, 2632 E. Washington St., Pasadena, Calif.

Richmond County Radiological Society
Secretary Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. John W. Colgan, 277 Alexander St., Rochester 18, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth St., Denver 20, Colo. Annual midsummer meeting: Shirley-Savoy Hotel, Denver, Colo., Aug. 15–17, 1957.

St. Louis Society of Radiologists
Secretary, Dr. Edwin C. Ernst, Jr., 3720 Washington Ave., St. Louis 8, Mo. Meets fourth Wednesday each month, except June, July, Aug. and Sept.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets Brooke Army Medical Center Officers Mess second Wednesday of each month.

San Diego Radiological Society
Secretary, Dr. J. C. Asher, 2001 Fourth Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Irma Smith, 450 Sutter St., San Francisco 18, Calif. Meets quarterly at Grison's Steak House.

Section on Radiology, California Medical Association
Secretary, Dr. A. R. Wilson, 540 North Central Ave., Glendale 3, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. J. Burbank, Meriden Hospital, Meriden, Conn. Meetings are held bi-monthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. Melvin O. Goodman, 1930 K St., N.W., Washington 6, D. C. Meets Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. George E. Irwin, Jr., 703 N. East St., Bloomington, Ill.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M. September to May inclusive.

Society of Nuclear Medicine
Secretary, Dr. Robert G. Moffat, B. C. Cancer Institute, 2656 Heather Street, Vancouver 9, Canada. Annual meeting to be announced.

South Bay Radiological Society
Secretary, Dr. Howard L. Jones, Palo Alto Hospital, Palo Alto, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. S. W. Lippincott, 103 Rutledge Ave., Charleston, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, Mobile, Ala.

Southwestern Radiological Society
Secretary, Dr. Gordon Black, Suite 2-A, El Paso Medical Center, 1501 Arizona, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. G. K. Henshall, 311 Medical Arts Bldg., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. J. E. Miller, Baylor Hospital, Dallas, Texas.

Tri-State Radiological Society
Secretary, Dr. Robert E. Beck, 600 Mary St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May, Service Memorial Institute.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Eva L. Gilbertson, 1317 Marion St., Seattle 4, Wash. Meets fourth Monday of each month from September through May at 610 Pine St., Seattle.

West Virginia Radiological Society
Secretary, Dr. W. Paul Elkin, 515 Medical Arts Bldg., Charleston, W. Va. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. M. G. Priestman, New Rochelle Hospital, New Rochelle, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Farrell F. Golden, 5221 Tonyawatha Trail, Madison, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-Ray Study Club of San Francisco
Secretary, Dr. J. T. English, 2000 Van Ness Ave., San Francisco 9, Calif. Meets monthly, third Thursday at 7:45 P.M., Lane Hall, Stanford University Hospital.

Cuba, Mexico, Puerto Rico and Central America

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San Jose, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, Mexico 7, D. F.
Secretary General, Dr. Guillermo Santín. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Diaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sanchez, Apartado No. 86, Panama, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Empire

Association of Radiologists of the Province of Quebec
Secretary, Dr. Isadore Sedlezky, 3755 Cote St. Catherine Rd., Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 P.M.
Medical Members' meeting, on third Friday in each month at 5:00 P.M., 32 Welbeck St., London, W 1

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Secretary, Dr. Isadore Sedlezky, 3755 Cote St. Catherine

Rd., Montreal, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicales
General Secretary, Dr. Ls Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

College of Radiologists (Australia and New Zealand)
Honorary Secretary, Dr. Alan R. Colwell, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W.

South America

Asociacion Argentina de Radiologia
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151 Córdoba, Argentina. Meetings held monthly.

Sociedad Argentina de Radiologia, Junta Central, Buenos Aires
Secretary, Dr. Oscar F. Noguera, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Argentina de Radiologia, Filial del Litoral, Sede, Rosario
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 19 ha 663 Italia St., Rosario, Santa Fe.

Sociedad Argentina de Radiologia, Filial del Sur, Sede, La Plata
President, Prof. Dr. Jose P. Uslenghi, La Plata. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Centro Sede, Córdoba
President, Prof. Dr. David L. Caro, Corro 86, Córdoba. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Norte, Sede, Tucuman
President, Dr. Julio Mendez Valladares, Rivadavia 358, Tucuman. Meets monthly.

Sociedad Argentina de Radiologia, Filial de Cuyo Sede, Mendoza.
President, Dr. J. A. Orfila, Hospital Central, Mendoza. Meets monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiologia
Secretary, Dr. Armando Doberti, Merced 565, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Luis E. Lozano B., Carrera 12 No. 20–69, 6° piso, Bogota, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiologia y Fisioterapia
Secretary, Dr. Enrique Ortega Guzmán, Casilla 4719, Guayaquil, Ecuador.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos G. Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary General, Dr. Roberto François, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad Venezolana de Radiología
Secretary, Dr. Otto Paz, Centro Médico, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Austrian Roentgen Society
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Société Française d'Electro-Radiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord
Secretary-General, Dr. A. Dariaux, 9 bis, Boulevard Rochechouart, Paris IX°, France.

Ceskoslovensk společnost pro rëntgenologii a Radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July August, and September. Annual general meeting.

Deutsche Röntgen-Gesellschaft
Secretary, Dr. med. Peter Kröker, Evangelisches Krankenhaus, Huyssens Stiftung, (22a) Essen.

Societa Italiana di Radiologia Medica
Secretary, Prof. Mario Ponzio, Ospedale Mauriziano, Torino, Italy. Meets biannually.

Nederlandse Vereniging voor Electrologie en Roentgenologie
Secretary, Dr. B. J. Rethmeier, Bornsestraat 378, Almelo Netherlands.

Polish Society of Radiology
Secretary, Dr. Juljusz Borejko, 59 Nowogrodzka St., Warsaw, Poland.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10:30, X-Ray Dept., Akademia Gdansk.

Wroclaw Section, Polish Society of Radiology
Secretary, Dr. R. Marciniak, Akad. Medyczna Wroclaw, 68 Curie-Sklodowska St., Wroclaw, Poland. Meets first Sunday of each month, X-Ray Department, Akademia Medyczna Wroclaw.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30 S.I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad
USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiologia y Electrologia
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société-Suisse de Radiologie)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The list of Meetings of Radiological Societies is published in every other issue of the Journal.

HICKEY MEMORIAL LECTURE 1957

The Annual Hickey Memorial Lecture was held in Detroit, Michigan under the joint sponsorship of the Wayne County Medical Society, the College of Medicine of the Wayne State University and the Detroit Roentgen Ray and Radium Society on March 14, 1957. Dr. John Caffey of the College of Physicians and Surgeons, Columbia University and Babies Hospital in New York spoke on "The Skeleton in Cooley's Anemia."

On this occasion, Dr. Grant Janes of Findlay, Ohio, unveiled a portrait of Dr. Lawrence Reynolds, Editor of this JOURNAL, painted by the great artist John S. Coppin of Bloomfield Hills, Michigan.

This portrait was presented to Dr. Reynolds by his former residents in "deep appreciation for his splendid teaching and guidance in the practice of the science of radiology."

THE ORGANIZATION OF THE INTERNATIONAL MEDICAL-SURGICAL MEETINGS

From June 1 to 9, 1957, the palace of "Torino-Esposizioni" will be open to physicians, surgeons and specialists in all fields of the medical sciences who will meet there for the Third International Medical-Surgical Meetings.

Of importance will be the International Congress on Nuclear Medicine, the International Congress on Photobiology and the International Congress of the Problems of Goiter. Of the seven national congresses, those on Chemotherapy and Gastroenterology and the Spring Session of the National Congress of the Italian Society of Surgery are worthy of particular note. The International Symposia include such events as the Symposium of the European Society of Cardiovascular Surgery, the Associated Meetings on Cardiosurgery and the Symposium on Artificial Heart-Lung Machine.

Those interested should write to: Segreteria Generale, Minerva Medica, Corso Bramante 83–85, Torino, Italy.

FOURTH ANNUAL MEETING OF THE SOCIETY OF NUCLEAR MEDICINE

The fourth annual meeting of the Society of Nuclear Medicine will be held June 20–23, 1957 at the Skirvin Hotel in Oklahoma City. An outstanding program of papers, speakers and exhibits is planned. The Oklahoma Centennial Exposition will also be in session at this time. Details may be obtained from: Dr. Robert W. Lackey, 452 Metropolitan Building, Denver, Colorado.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

ROENTGEN SIGNS IN CLINICAL DIAGNOSIS. By Isadore Meschan, M.A., M.D., Professor and Director of the Department of Radiology at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina; with the assistance of R. M. F. Farrer-Meschan, M.B., B.S. (Melbourne, Australia). Cloth. Price, $20.00. Pp. 1,058, with 2,216 illustrations on 780 figures. W. B. Saunders Company, West Washington Square, Philadelphia 5, Pennsylvania, 1956.

Do we need another textbook of roentgen diagnosis? Anyone seeing Meschan's *Roentgen Signs in Clinical Diagnosis* for the first time might well make this query. Until one has read through this volume, however, the full implication of his title is not felt. The book presents the fundamentals of roentgenology arranged on the basis of objective signs as seen in roentgenograms. The text is organized to promote some idea of the limitations as well as the accuracy in roentgen diagnosis, pointing up the anatomic and physiologic basis of roentgen signs in disease. It is organized to lead the reader to systematic thinking and analysis of the roentgen signs prior to the formation of a definitive diagnosis. This type of thinking is certainly particularly applicable to residents in radiology and all other students of this science, for that matter.

Dr. Meschan considers his treatise in three phases. Phase one is a presentation of normal anatomy. Phase two presents the roentgen signs of disease, the signs being classified in terms of change in size, contour, architecture, density, position, and function. In the third phase the criteria in phase two are assembled in sections and are used in the form of differential diagnostic possibilities in arriving at a correct diagnosis.

Typifying this approach are three chapters on bone disease which are entitled "Radiolucent Bone Disease of Multiple Extremities," "Radiolucent Bone Disease of a Single Extremity," and "Osteosclerotic and Hypertrophic Bone Diseases of the Extremities." Each of these chapters is further divided and in the subdivisions specific generalized and localized diseases are discussed in detail, roentgen features being illustrated by excellent line drawings and characteristic roentgenograms.

Chapter 8, "Radiolucent Bone Diseases of Multiple Extremities," exemplifies this work. The chapter is subdivided as follows:

I. Radiolucencies occurring in multiple metaphyses primarily.
II. Radiolucent bone disease of extremities affecting the skeleton in diffuse or scattered fashion.
   A. Diseases causing generalized radiolucency of the extremities.
   B. Diseases causing multiple areas of circumscribed osteoporosis of the extremities.
   C. Diseases causing multiple linear areas of osteoporosis in the extremities and apparent coarsening of the trabeculae.

These groups are further divided and subdivided until each disease process is individually discussed and illustrated.

"Key" references are scattered throughout the text in appropriate places and, in addition, general references are appended to each chapter. The key references have been carefully selected and represent up-to-date significant contributions with which every student of radiology should be familiar.

If any criticism could be leveled at this fine book it would be that so much material has been encompassed in its pages that the medical student and casual student of radiology might find it overwhelming. The earnest radiologic resident and practicing radiologist will appreciate its completeness and scope.

HAROLD FULTON, M.D.

CLINICAL ROENTGENOLOGY. VOLUME IV. THE DIGESTIVE TRACT, THE GALL BLADDER, LIVER AND PANCREAS, THE EXCRETORY TRACT AND SPECIAL STUDIES EMPHASIZING DIFFERENTIAL CONSIDERATIONS. By Alfred A. de Lorimier, M.D., Radiologist, Saint Francis Memorial Hospital, San Francisco, California; Henry G. Moehring, M.D., Radiologist, Duluth Clinic, Duluth, Minnesota;

and John R. Hannan, M.D., Radiologist, Cleveland, Ohio. Cloth. Price, $24.50. Pp. 764, with 1,112 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1956.

The fourth volume of this textbook maintains the general plan and arrangement adopted in the previous volumes. The emphasis is again on clarity, brevity and pictorial demonstration rather than completeness. In spite of this obviously deliberate limitation, the volume contains a wealth of information and is, like its predecessors, an excellent guide, particularly for the graduate student. The authors have cultivated and made good use of their gift to explain highly complex matters in simple terms.

The scope of Volume IV is tremendous—the entire digestive tract, the biliary system, the urinary tract and obstetrical roentgenology. This whole field is adequately covered. Each chapter deals with the basic physiologic, anatomic and pathologic features, with the roentgen manifestations, clinical and laboratory corroborations and differential diagnosis of the diseases under discussion. The various abnormalities are exemplified by well chosen illustrations with excellent captions. Indeed, the book is so composed that if the reader looked only at the illustrations he would considerably add to his knowledge.

It is inevitable that within the general framework of this treatise complete or detailed analysis plays only a secondary role. After familiarizing himself with the subjects discussed in this volume, the student will still have to peruse many publications in order to understand what he is trying to do; but the references quoted are not always sufficient to lead him towards the most valuable information obtainable. For instance, in the chapter on megacolon the work of Swenson and his Boston associates is not cited.

Whether one likes or dislikes this textbook will depend on his being interested in mass roentgenology or the care of individuals. The present trend is towards mass roentgenology. This volume helps significantly to make mass roentgenology a useful procedure, which is a step in the right direction, no matter whether one deplores or welcomes the trend.

The book is well printed, the illustrations are far superior to what we used to see in American publications, and the index is adequate. This volume is recommended as a basic text particularly suited to the needs of graduate students and residents.

Albert Oppenheimer, M.D.

BOOKS RECEIVED

Bladder Tumors: A Symposium. Under the auspices of The American Cancer Society. Cloth. Price, $4.00. Pp. 92, with numerous illustrations. J. B. Lippincott Company, East Washington Square, Philadelphia 5, Pennsylvania, 1956.

Clinical Use of Radioisotopes. By William H. Beierwaltes, M.D., Associate Professor of Internal Medicine and Coordinator, Clinical Radioisotope Unit, University Hospital, Ann Arbor; Philip C. Johnson, M.D., Assistant Professor of Internal Medicine and Chief, Radioisotope Unit, Veterans Administration Hospital, Oklahoma Medical School, Oklahoma City; and Arthur J. Solari, B.S., M.S. (Physics), Instructor in Radiation Physics, Department of Radiology, Radiation Physicist for Clinical Radioisotope Unit and Kresge Research Isotope Unit, University Hospital, Ann Arbor. Cloth. Price, $11.50. Pp. 456, with 126 illustrations. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, Pennsylvania, 1957.

The Treatment of Fractures. Volume II. By Lorenz Böhler, M.D., Director of the Accident Hospital, Vienna; Professor of Accident Surgery, University of Vienna. Translated from the Thirteenth German Edition by Otto Russe, M.D., Director of the Accident Hospital, Vienna, and R. G. B. Bjornson, M.D., Diplomate, American Board of Radiology. Cloth. Price, $17.50. Pp. 1,508, with 2,166 illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, New York, 1957.

The Physician-Writer's Book—Tricks of the Trade of Medical Writing. By Richard M. Hewitt, A. M., M.D., Senior Consultant, Section of Publications, The Mayo Clinic; Associate Professor of Medical Literature, The Mayo Foundation, Graduate School, University of Minnesota. Cloth. Price, $9.00. Pp. 415, with 37 illustrations. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, Pennsylvania, 1957.

The Year Book of Radiology (1956–1957 Series). Radiologic Diagnosis edited by John Floyd Holt, M.D., Professor, Department of Radiology, University of Michigan; and Fred Jenner Hodges, M.D., Professor and Chairman, Department of Radiology, University of Michigan; Radiation Therapy edited by Harold W. Jacox, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Morton M. Kligerman, M.D., Associate Professor

of Radiology, College of Physicians and Surgeons, Columbia University; Associate Attending Radiologist, Presbyterian Hospital, New York City. Cloth. Price, $9.00. Pp. 430, with 361 illustrations. The Year Book Publishers, Inc., 200 East Illinois Street, Chicago, Illinois, 1957.

PEDIATRIC CARDIOLOGY. By Alexander S. Nadas, M.D., F.A.A.P., Assistant Clinical Professor of Pediatrics, Harvard Medical School; Cardiologist, The Children's Hospital; Physician, Sharon Cardiovascular Unit, Children's Medical Center, Boston. Cloth. Price, $12.00. Pp. 587, with 343 illustrations. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, Pennsylvania, 1957.

I QUADRI RADIOLOGICI DELLE GASTRITI. RELAZIONE AL LVII CONGRESSO DELLA SOCIETA ITALIANA DI MEDICINA INTERNA, MILANO—OTTOBRE 1956. By Prof. Alessandro Vallebona, with the collaboration of Prof. Luigi Oliva. Paper. Pp. 83, with numerous illustrations. Ditta Luigi Pozzi, Editore, Via Sistina, 14, Rome, Italy, 1956.

Vol. 77, No. 5

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Head

Jackson, Harris. (Johannesburg, South Africa.) Asymmetry and growth of the skull; the Barclay prize essay, 1956. *Brit. J. Radiol.*, Oct., 1956, *29*, 521–535.

Perfect skull asymmetry about the sagittal plane does not occur; therefore, it is essential to differentiate between physiologic and pathologic asymmetry. For this purpose asymmetry must be sought and analyzed, and a knowledge of the factors influencing skull growth becomes essential.

For an adequate study of asymmetry at least the following views are needed: lateral, Towne-Twining, basal and "sphenoidal fissure" (vertico-mental view projecting the sphenoidal fissure into the orbits). In the posteroanterior projection the roentgenographic base line is perpendicular to the film and the central ray, angulated from 8 to 25 degrees to the feet, emerges through the nasion. The importance of adequate and correct positioning is stressed. However, although rotation may cause apparent displacement of a calcified pineal gland, the fact that it is not true displacement should not be difficult to determine.

The author presents the following classification of cranial asymmetry which is used as a basis for evaluating cases under consideration:

1. *Intracranial Causes:*
   (a) Excessive growth stresses:
      (i) Extracerebral, *e.g.* chronic subdural hematoma, aneurysm of the internal carotid artery.
      (ii) Intracerebral, *e.g.* slow-growing tumors, infiltrating lesion and cysts.
   (b) Deficient growth stresses:
   e.g. the cerebral atrophies, including Sturge Weber syndrome.
2. *Cranial Causes:*
   (a) Deficient growth at the sutures, *i.e.* craniostenosis
   (b) Excessive growth, ? analogous to hemivertebrae
3. *Extracranial Causes:*
   These may be endogenous or exogenous stresses, or a combination of the two, *e.g.* with prolonged recumbency, torticollis, etc.

The author carefully reviews significant articles which appeared in the literature and presents a number of illustrative cases.

Quoting Dyke and Davidoff, the author lists the following signs of a subdural hematoma:

1. Elevation of the sphenoid ridge, the superior orbital plate and the superior orbital ridge.
2. Deepening, widening and lengthening of the middle fossa.
3. Disappearance or indistinctness of the oblique line in the orbit (the linea innominata).
4. Atrophy of the superior and lateral wall of the superior orbital fissure.
5. Hypertrophy of the frontal and ethmoid sinuses.
6. Thickening of the skull.

Quoting Dyke, Davidoff, and Mason, the following signs of unilateral cerebral atrophy are listed:

1. Thickening and smallness of one side of the vault.
2. Hypertrophy of the ipsilateral ethmoid, frontal and temporal air cells.
3. Elevation of the orbit and of the petrous bone on the same side.

To which he adds the following, by McRae:

4. Smoothness of the petrous ridge.
5. Displacement of the groove for the superior sagittal sinus and of the crista galli.

The author evaluates the relative incidence of these signs in 34 cases of known cerebral atrophy. All of these signs occurred in one case. However, thickening and smallness of one side of the vault with an accompanying loss of convolutional markings were the most prevalent signs and were found to be reliable evidence of cerebral atrophy.

Elevation of the orbit and of the petrous bone were the next most common findings.

Considerable variation in the position of the lesser wing of sphenoid was noted in 8 cases of marked hemicranial atrophy—3 elevated, 3 depressed, and 2 symmetrical.

Evaluation of asymmetry in terms of vital reaction of the skull is considered more significant than actual measurements or tracings. The size and shape of the bone, such as the skull, depends on its inherent growth potential, its ability to react to stresses and strains and the stimuli to which it is subjected.

Enlargement of the skull, widening of the sutures, and thinning of the inner table are due to localized reaction to the growth of the immediately subjacent tissues rather than to diffuse intracranial pressure in the usual hydrostatic sense.

In conclusion the author stresses the following points:

1. Thinning of the inner table is due to the apposition of a growing fluid or solid mass, *e.g.* normal and abnormal convolutional impressions, localized absorption with a porencephalic cyst, and generalized absorption with a chronic subdural hematoma. Pulsation may be a factor in producing this thinning, but it is less important than apposition and growth.

2. Thickening of the inner table occurs when the brain tends to fall away from it. This thickening is effected by the endosteum.

3. The position of the lesser wing of the sphenoid is dependent mainly on growth at the temporoparietal sutures, and only to a lesser extent on growth in the anterior and middle fossae and in the orbit.

4. The pressure of growth of the intracranial contents is neither hydrostatic nor distributed according to Pascal's law of pressure in a fluid.

5. A porencephalic cyst may be a region of posi-

tive growth producing thinning of the inner table.

Two tables and reproductions of 18 roentgenograms and diagrams accompany this article.—*William H. Shehadi, M.D.*

Schäfer, H. Beitrag zur Schädelossifikation bei der Dysostosis cleidocranialis. (Ossification of the skull in cleidocranial dysostosis.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1956, *85*, 309–316. (Address: Heubnerweg 6, Berlin-Charlottenburg 5, Germany.)

A case of this disease, observed from birth until the age of sixteen months, is described in detail and roentgenograms of the skull at various ages are reproduced. The ossification of the cranial bones was markedly delayed and, according to the author, corresponded at birth to the degree of ossification of a fetus of three months. The clavicles, vertebral column and pubis were also involved. This case is one of the few described in newborns.

The process of ossification of the cranial bones, which in normal fetuses takes place in utero and thus is difficult to observe roentgenagraphically, is beautifully demonstrated in the series of roentgenograms obtained on this child.

Six roentgenograms and a drawing showing the progress of ossification of the skull during sixteen months of observation are reproduced. A fairly large bibliography is included.—*Karol E. Matzinger, M.D.*

Riley, Patrick, Stuteville, Orion, and Brown, Robert C. Familial fibrous swelling of the jaws; a new case. *Radiology*, Nov., 1956, *67*, 742–745. (Address: R. C. Brown, 3609 South Court, Palo Alto, Calif.)

A case of familial fibrous swelling of the jaws in a a five-year-old boy is reported. This patient had generalized enlargement of the jaws with the maxillae being particularly prominent. The alveolar ridges were widened, and irregular spacing and poor alignment of the teeth had developed in the last few months. Roentgen studies showed a multilocular cystic appearance of the mandible and a diffuse increase in density of the maxillae which were moderately enlarged and encroached upon the maxillary sinuses. The deciduous teeth were poorly aligned and had rudimentary roots, and the dental follicles for the permanent teeth were irregularly placed and abnormal in size. Biopsy of the jaw showed findings consistent with familial multilocular cystic disease of bone.

This is believed to be the tenth recorded case of this unusual condition and displays all the findings observed in the earlier cases. The patient's father and uncle both gave a history and findings suggesting a similar process in their youth. The onset of this abnormality seems to parallel the beginning of resorption of deciduous tooth roots, suggesting "overaction" of normal resorptive processes with resultant pseudocysts which fill with fibrous tissue.—*Harold C. Hamilton, M.D.*

Wells, Paul O. The button sequestrum of eosinophilic granuloma of the skull. *Radiology*, Nov., 1956, *67*, 746–747. (Address: Harlan Memorial Hospital, Harlan, Ky.)

Although several excellent articles have appeared in the literature on the subject of eosinophilic granuloma of the skull, only one has specifically called attention to the rather characteristic sequestrum produced in some of these cases. This sequestrum appears as a "button" of intact bone in the center of a circular area of destruction. Such a sequestrum formation has been found by the author upon roentgenographic examination of 4 proved cases of eosinophilic granuloma.

The patients considered in this study were males in the third decade of life. All complained of a tender or painful area in the scalp. Physical findings and laboratory studies were generally normal, except for an eosinophilia of 9 per cent in one patient and 8 per cent in another. On roentgenographic examination an osteolytic area involving both tables of the calvarium was noted. No expansion of bone or periosteal new bone formation was seen. The previously described "button" sequestrum was present in all instances. It is pointed out that while tuberculous osteomyelitis and possibly post-traumatic fibrous changes in the bone may sometimes show similar changes, the finding of an osteolytic skull lesion containing a central sequestrum is suggestive of an eosinophilic granulomatous lesion. The author believes that the sequestrum formation is more common in this condition than has previously been recognized.—*A. Ralph Watson, M.D.*

Dunn, Jack, Jr., and Holman, Colin B. The incidence and roentgenographic significance of calcification in the choroid plexus of the lateral ventricle. *Proc. Staff Meet., Mayo Clin.*, Feb., 1956, *31*, 100–104. (From: Department of Neurosurgery, and Section of Roentgenology, Mayo Clinic, Rochester, Minn.)

Roentgenographic evidence of calcification of the choroid plexus of the lateral ventricle must be considered in the differential evaluation of both pathologic and physiologic intracranial calcifications. Reported early in 1903 by Oppenheim, the most common site of choroid calcification seems to be located at the enlarged genu of the lateral ventricle within the glomus.

Choroid calcium deposits may attain a diameter of 1 cm. or more and when bilateral will appear as an inverted isosceles triangle in its relation to pineal

calcification. In the lateral view the calcified portion of the choroid plexus lies about 1 cm. behind and 0.5 cm. above the pineal shadow. In the posteroanterior view it lies about 2.5 cm. lateral to the midline.

Pathologic intracranial calcification due to gliomas, meningiomas, hemangiomas, dermoids, hematomas, tuberculous parasitic cysts, old abscesses, chronic encephalitis and arteriovenous malformations may be confused with physiologic calcification of the choroid glomus. Not to be forgotten are calcifying meningiomas arising within the choroid plexus itself, and the calcium deposits found occasionally in the basal ganglia. Unilateral choroid calcification may simulate a markedly shifted pineal or deep seated glioma. Mobility of the choroid density with changes in the position of the head may cause an asymmetric position of the 2 plexuses and falsely suggest the presence of a space occupying lesion and require pneumography for differentiation.

The general incidence of choroid calcification has been reported as varying from 5 to 30 per cent. In a group of 324 brains obtained at postmortem, varying from birth to one hundred years of age, there were 28 examples of glomus calcification visualized by roentgen studies of the gross specimens. These represented 8.6 per cent of the total. Calcium deposition was never found in any other portion of the choroid plexus except the glomus. The youngest person was twenty years of age and the oldest was ninety-four. Six were less than sixty years of age, but 78.6 per cent were over sixty. Males predominated 2 to 1.

Unilateral calcification was found in 4 of 28 cases, or 14.2 per cent. In these, faint traces of calcium deposits were seen in the opposite plexus, but were of sufficient quantity to be visualized roentgenographically. Microscopic examination invariably showed greater quantities than were seen roentgenographically, and these deposits were contained within psammoma bodies and hyaline plaques in the villi, indicating regressive changes.—*J. A. Campbell, M.D.*

Neck and Chest

Simpson, S. Aaron, Gordon, Sewell S., Jorgens, Joseph, and Rigler, Leo G. Roentgen changes following radical neck dissection. *Radiology*, Nov., 1956, *67*, 704–713. (Address: VA Hospital, Minneapolis 17, Minn.)

Roentgen changes following radical neck dissection are described and demonstrated. The results of an analysis of 33 cases are reported. Six more or less specific changes were noted in the posteroanterior roentgenograms of the chest.

Loss of the sternomastoid shadow was the most frequent change, but was also the least striking of the alterations. There was a relative increase in radiability of the apex and a regional soft tissue defect in about 70 per cent of the cases. This finding is due to a loss of soft-tissue mass and a consequent decrease of the thickness through which the roentgen rays must penetrate.

Dropping of the shoulder was found in two-thirds of the cases. This is due in part to excision of the sternomastoid muscle, but is primarily the result of destruction of the eleventh nerve innervating the trapezius muscle. If the nerve was intact, the shoulder sign was not observed. Clavicular periosteal reaction, presumably due to surgical trauma to the clavicular periosteum, was seen in 5 cases. Diaphragmatic paralysis, due to accidental injury to the phrenic nerve, was seen 4 times.

The practical aspects of the identification of this procedure are discussed.—*A. W. Sommer, M.D.*

Steiner, Howard A. Aplasia of the lung; a case report. *Radiology*, Nov., 1956, *67*, 751–753. (Address: 291 Buhl Blvd., Sharon, Pa.)

Aplasia and agenesis of the lung are rare conditions. In agenesis of the lung, the anomaly ranges from complete absence of a lung, with its main bronchus, to a condition in which a rudimentary bronchus and varying amounts of pulmonary tissue are present. This latter condition is more appropriately called aplasia of the lung.

The diagnosis is made by roentgenographic, bronchoscopic, and bronchographic examination. The chest roentgenogram shows incomplete or total absence of aeration on the affected side of the thorax. The thorax on this side is flattened, the intercostal spaces are narrowed and the diaphragm may be elevated. Other congenital anomalies may also be seen roentgenographically. Since pulmonary atelectasis, a plugged bronchus, tumor, bronchiectasis or a tuberculous stricture may cause a similar roentgen appearance, bronchoscopy should be employed to rule them out. Bronchography will outline the aerated portions present. Aplasia or agenesis is not incompatible with life, as patients with this condition have lived for over fifty years, and have died from other causes. Death, however, has occurred in almost 50 per cent of the cases reported in the literature, usually in the first five years of life, and due in most cases to infection.

The author presents a case report of aplasia of the right lung in a newborn infant, with autopsy confirmation. The diagnosis was made by bronchography which revealed a short narrow bronchus terminating in a small amount of alveolar tissue.—*Donald N. Dysart, M.D.*

Cimmino, Christian V. The esophageal-pleural stripe on chest teleroentgenograms. *Radiology*, Nov., 1956, *67*, 754–756. (Address: Mary Washington Hospital, Fredericksburg, Va.)

The author calls attention to a shadow of soft-tissue density, seen at times on the posteroanterior

chest film, superimposed directly upon the gas shadow of the trachea. It was found in 25 of a consecutive series of 200 chest examinations.

This shadow does not represent an abnormality. It follows exactly the course of the barium-filled esophagus. The author believes that this shadow represents the mediastinal (parietal) and visceral pleura with any intervening capillary fluid, in addition to the major component, the right esophageal wall, which varies in thickness according to its functional state. Its presence on 6 foot chest roentgenograms should be more widely known, especially since the trend is toward higher voltages, if only to avoid error in imputing pathologic significance to it.—*A. W. Sommer, M.D.*

Keats, Theodore E. Pantopaque pulmonary embolism. *Radiology*, Nov., 1956, *67*, 748–750. (Address: Department of Radiology, University of Missouri College of Medicine, Columbia, Mo.)

Pantopaque pulmonary embolus is a rare complication of myelography, only 4 cases of venous intravasation during this procedure having been reported. In 2 of these 4 cases, pulmonary embolus was demonstrated by visualization of the opaque medium on the chest roentgenogram.

The author reports an additional case of this complication, in which the pulmonary embolization was demonstrated. The venous intravasation may occur either during the injection of the opaque medium, or during its aspiration. In this particular patient the embolization occurred during aspiration. There was immediate chest pain and a violent unproductive cough, which lasted about thirty minutes. Following a febrile episode of several days, recovery was complete. Chest roentgenograms made immediately following the embolization showed a finely granular pattern of the opaque medium in both lower lung fields.

It is thought that between 4 to 7.5 cc. of pantopaque must enter the venous system for it to be visualized roentgenographically. It was estimated that about 7 cc. of the medium was embolized in this case.—*Donald N. Dysart, M.D.*

Reindell, H., Musshoff, K., and Klepzig, H. Regulative und myogene Dilatation des Herzens; Versuch einer Neueinteilung. (Regulative and myogenic dilatation of the heart; an attempt at a new classification.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1956, *85*, 385–408. (From: Medizinische Universitätsklinik, Freiburg i. Br., Germany.)

In this 20 page long article the authors set forth some new ideas about dilatation of the heart. They investigated the function of the heart in humans at rest and during exercise by several different methods: roentgenographic determination of shape and size, kymographic examination, determination of blood volume and pressure changes, cardiac catheterization in some cases, electrocardiography, spiroergometry and, in a few instances, histologic examination. They found that the theories of Frank, Straub and Starling gained by experiments on the isolated heart are, during life, applicable only to hearts with a damaged myocardium. When the heart muscle is normal and functions normally and when a regulative dilatation takes place physiologically, as in sportsmen, the dilatation is secondary to physiologic hypertrophy of the muscle. Such hypertrophy with regulative dilatation may be found also in valvular disease without muscle disease. It is usually present not only in the ventricles but also in the auricles.

These observations indicate that a normal heart may change in shape and size considerably without abnormal changes in the muscle. If there is a diseased or damaged myocardium, the dilatation is of myogenic origin. Because of the insufficient contractions the intracardiac pressure causes a dilatation of the heart as predicted by the theories gained from experiments on the isolated heart. These two types of dilatation should be differentiated because of their different etiology and significance.—*Hans W. Hefke, M.D.*

Milatz, W. Die anuläre Sklerose der Ventilebene des Herzens und die Verkalkung der Herzklappen. Ein Beitrag zur Differentialdiagnose intrakardialer Verkalkungen. (Annular sclerosis of the valve level of the heart and calcification of the valves of the heart. A contribution to the differential diagnosis of intracardiac calcifications.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1956, *85*, 282–292. (Address: Seestrasse 27, Potsdam, Germany.)

To demonstrate intracardiac calcifications, fluoroscopy with a fairly hard beam and exposures with high voltage are required. The factors recommended for roentgenography are: 120 kv., 4–8 ma., 0.05 sec. Calcifications in the rings and valves show greatest pulsations in the right anterior oblique projection. The pulsations exceed in amplitude those of the left heart border.

Two cases with calcifications in the mitral ring and the mitral and aortic valves are described in detail.

The article contains numerous references and reproductions of 6 roentgenograms.—*Karol E. Matzinger, M.D.*

Abdomen

Goin, Lowell S., and Wilk, Stefan P. Intermittent arteriomesenteric occlusion of the duodenum. *Radiology*, Nov., 1956, *67*, 729–

737. (Address: L. S. Goin, 658 South Westlake Ave., Los Angeles, 43, Calif.)

Arteriomesenteric occlusion of the duodenum is a rather rare clinical entity characterized by intermittent obstructive symptoms. It occurs mostly in patients of the asthenic habitus and is to be differentiated from duodenal stasis which is organic in nature. A positive diagnosis can be made only by careful fluoroscopic examination. With the patient erect, fluoroscopy usually discloses a rather long, vertical type of stomach, with dilatation of the proximal duodenum to the mid-line, where there is an abrupt obstruction of the third portion of the duodenum as it crosses the spine. The dilated portion exhibits strong, churning peristalsis, reverse peristalsis being quite prominent. If the patient is placed in the prone position, the duodenal retention usually disappears more or less completely—assumption of the knee-chest position or pressure over the lower abdomen has a similar effect—but with return to the erect position the stasis recurs. Spot films at the site of obstruction show a narrow, compressed lumen, but normal mucosa can usually be demonstrated.

Attention is called to certain diagnostic pitfalls. Churning peristalsis of the duodenum is not a pathognomonic sign, since it is seen in various conditions. A moderate dilatation of the duodenum, with delay in passage through the transverse portion, is observed in many thin patients examined in the supine position, but it commonly disappears with resumption of the erect posture. Occlusion caused by tumors, congenital bands, malrotation of the intestine, adhesions, etc., must be considered in the differential diagnosis. It must also be remembered that arteriomesenteric occlusion of the duodenum is intermittent in nature, and often repeated examinations are necessary before the diagnosis can be made.

Therapy in this disorder consists of either medical and postural or surgical treatment. Many patients will be relieved on medical management. If surgical treatment must be resorted to, the operation of choice is duodenojejunostomy. Gastroenterostomy is definitely contraindicated and gives poor results.

Six cases of arteriomesenteric occlusion of the duodenum are discussed and characteristic roentgenograms are reproduced.—*A. Ralph Watson, M.D.*

Wise, Robert E., and O'Brien, Richard G. Interpretation of the intravenous cholangiogram. *J.A.M.A.*, March 10, 1956, *160*, 819–827. (Address: R. E. Wise, 605 Commonwealth Ave., Boston 15, Mass.)

This study comprises a series of 300 cases in which intravenous cholangiography was carried out using cholografin (sodium iodipamide). The study was undertaken in an effort to determine the significance of the various degrees of dilatation of the common duct and to establish criteria for accurate preoperative diagnosis of the various degrees of obstruction of the common duct.

The patient is usually examined in the morning in a fasting state after cleansing of the intestine with castor oil. Patients were given 40 cc. of a 20 per cent solution in most instances, (in 30 cases 20 cc. of 40 per cent solution was used with no significant difference in time or degree of opacification of the ducts). The patient is placed in the supine position with the left side elevated approximately 15 degrees. Roentgenograms are made serially every ten to fifteen minutes throughout a period of at least two hours, in the majority of cases. If the gallbladder is present or visualized, the examination is carried out to full opacification of the gallbladder. Each film is viewed immediately by the radiologist, and technical factors are adjusted as necessary.

The authors analyzed the various liver function tests and their relation to duct visualization. Neither the sulfobromophthalein retention test, nor the serum bilirubin concentration, afforded a basis for predicting whether the duct would be made visible by the sodium iodipamide. However, visualization never occurred when the serum bilirubin level was above 4.8 mg., or when the sulfobromophthalein retention was above 64 per cent.

In 142 patients the bile passages were successfully visualized after cholecystectomy, so that the diameter of the common duct could be measured. These data were compared with the results of actually exploring the duct for obstructions. All ducts dilated to a diameter greater than 15 mm. were found to be partially obstructed, and all those narrower than 8 mm. were unobstructed. The 82 ducts of intermediate diameter (57 per cent of the visualized cases) thus formed an important group in which the diameter of the duct was of no value in determining whether the duct was obstructed.

Intravenous injection of sodium iodipamide visualized the gallbladder in 12 out of 34 patients in whom visualization was poor or nil when the medium was given orally.

The most obvious use of this procedure is in visualization of common duct calculi, but it became apparent quite early in the authors' experience that determination of the presence or absence of partial obstruction of the common duct was of considerably more importance. It is the obstruction to the free flow of bile through the common duct, whether the obstruction be due to calculus, stricture, fibrosis of the sphincter of Oddi, or other cause, that is usually responsible for postcholecystectomy symptoms. The determination of this obstruction constitutes the most valuable application of intravenous cholangiography.—*William M. Loehr, M.D.*

Stenhouse, David. On the relative merits of the oral and intravenous methods of cholegraphy. *Brit. J. Radiol.*, Sept., 1956, *29*, 498–

503. (From: Radiodiagnostic Department, Western Infirmary, Glasgow, Scotland.)

In an attempt to evaluate the relative merits of the oral and intravenous methods of cholegraphy the author examined 100 patients using biligrafin on the first day and telepaque on the next day. The techniques are used in accordance with what has been accepted as "standard" for both methods. Laminagraphy was employed in a few cases where the bile ducts were obscured by overlying intestinal shadows.

Routinely the examination with biligrafin was stopped at two hours. The density of the gallbladder shadow was less than with telepaque; however, of 10 patients who were examined five hours later, 6 showed gallbladders with markedly increased density which was more than that produced by telepaque.

In abnormal cases special attention was paid to (a) the value of each method in the diagnosis of calculi, and (b) the significance of complete absence of gallbladder shadow after successive administration of each of the two contrast media.

Calculi in the gallbladder were better demonstrated when telepaque was used and the conclusion is that telepaque is much more accurate than biligrafin for this purpose. The absence of gallbladder shadow occurred in 20 cases when both telepaque and biligrafin were administered. In 2 cases the gallbladder was well visualized with telepaque, but not with biligrafin, and in one case was well visualized with biligrafin, but not with telepaque.

The factors contributing to the absence of gallbladder shadow when telepaque is used are: (a) failure of absorption due to gastrointestinal disease; (b) hepatic dysfunction—obstructive jaundice, cirrhosis; (c) disease of the gallbladder, impacted cystic duct calculi and tumor of the gallbladder.

Absence of gallbladder visualization when biligrafin is used may be due to one or more of the following causes: (a) disturbance in formation of blood protein; (b) hepatic dysfunction; (c) gallbladder disease—same as with telepaque.

It is further concluded that in the presence of visualization of the bile ducts, the absence of a gallbladder shadow is reliable evidence of gallbladder disease or occlusion of the cystic duct.

Biligrafin should be used when the gallbladder has been removed and when the examination must be completed within the same day.

In all cases the examination should start with telepaque. If visualization of the gallbladder and ducts should not occur then further use of biligrafin would be indicated so as to complete the examination. The two methods are considered complementary.

Reproductions of roentgenograms of five cases and one table accompany this article.—*William H. Shehadi, M.D.*

Anderson, F. G. Cholecystangiography using biligrafin forte. *Brit. J. Radiol.*, Sept., 1956, *29*, 504–507. (From : Walton Hospital, Liverpool, England.)

The introduction, in 1953, of intravenous biligrafin (20 per cent solution of the sodium salt—known as cholografin in the U.S.A.) marked a new approach to the roentgenologic investigation of the biliary tract. The dose is 40 cc.

The methylglucamine salt has since been introduced in 30 per cent solution (dose 20–40 cc.) and more recently in 50 per cent solution—biligrafin forte, dose 20 cc. (cholografin methylglucamine—52 per cent is the preparation used in this country, dose 20 cc.).

The author's report, based primarily on 33 examinations of 31 patients, leads to the conclusion that (1) the gallbladder and ducts are frequently visualized when they fail to be visualized with the 20 per cent preparation; (2) the bile ducts are more clearly defined, with greater contrast, and remain outlined much longer, so that the gallbladder and the ducts can be visualized simultaneously; (3) as in the case of its predecessor, this medium produces a good shadow of the gallbladder when the latter was only faintly visualized with telepaque or did not visualize at all.

The use of a 40 cc. dose of biligrafin forte presents no advantage over a 20 cc. dose.

One table and reproductions of seven roentgenograms accompany this article.—*William H. Shehadi, M.D.*

Gynecology and Obstetrics

Worm, M. Zur röntgenologischen Längenbestimmung des Kindes in utero. (Roentgenologic determination of fetal length in utero.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1956, *85*, 320–325. (Address: Diabetikerheim, Kreis Greifswald, Karlsburg, Germany.)

This procedure is considered to be of help in estimation of fetal age and in determining probable viability of the fetus of diabetic mothers where delivery before term is planned. A minimum fetal length of 48 cm. is postulated by some authors, while others consider roentgenographic demonstration of the distal femoral epiphyseal nucleus as necessary, before delivery of the fetus of a diabetic mother.

The author reports on his experience with measurements of fetal length in 77 pregnant diabetics and 4 patients with glycosuria during pregnancy. The method of Wegrad (*Zentralbl. Gynaek.*, 1937, *61*, 7, 373) was used, for the details of which the original article should be consulted. Briefly, the method is as follows: A single roentgenogram is obtained in

the prone position at 125 cm. focus-film distance and the length of the fetal spine is measured on the roentgenogram with a lead wire. The true length is calculated by correcting the measured length for magnification and multiplying by 2.29.

The calculated length of the fetal spine was checked by direct measurements after delivery and in half the cases the 2 figures agreed within 0.5 cm. The maximum deviation was 1.4 cm.

The distal femoral nucleus was visible in two-thirds of the fetuses, but was absent in some fetuses of diabetic mothers of over 50 cm. length of the spine, which in the author's opinion shows the limited value of this sign of maturity in fetuses of diabetics.—*Karol E. Matzinger, M.D.*

Skeletal System

Langelier, L.-P. (Arthabaska, Quebec.) Osteopetrosis; report of three cases. *J. Canad. A. Radiologists*, Dec., 1955, *6*, 51–58.

The author reports 3 cases which exhibited the classic findings of osteopetrosis. Two of the patients, who were siblings eleven and eighteen years of age, had the severe form of the disease with anemia and cranial nerve impairment. The third patient, an eleven year old girl, had the mild form with no involvement of the skull and slight anemia.

All 3 patients had osseous fragility and the characteristic roentgen findings including: (1) bilateral symmetrical sclerosis of bones with narrowing of the medullary canal; (2) clubbing of the ends of the long bones; (3) alternating rings of increased and decreased density in the iliac bones; and (4) transverse and longitudinal striations, particularly in the metaphyseal portion of the bones. The 2 patients who had the severe form of the disease had extensive involvement of the skull with thickening of the calvarium, thickening of the clinoid processes, obliteration of the paranasal sinuses and mastoid air cells, and in one case hypoplasia of the mandible.—*D. D. Peterson, M.D.*

Schneider, U. Das akzessorische Iliosakralgelenk (Articulus sacroiliacus accessorius) im Röntgenbild. (The accessory iliosacral joint and its roentgen appearance.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1956, *85*, 426–432. (Address: Ziemssenstr. 1a, München 15, Germany.)

Accessory iliosacral joints, independent and not connected with the main joint, have been described by anatomists and roentgenologists. The author found evidence of such an anomaly in 14 per cent of 1,100 roentgenograms of the pelvis. He could demonstrate them best on anteroposterior laminagrams.

The presence of such an anomaly is apparently of no clinical significance.—*Hans W. Hefke, M.D.*

Levin, Emanuel J. Congenital biliary atresia with emphasis on the skeletal abnormalities. *Radiology*, Nov., 1956, *67*, 714–722. (Address: Cincinnati General Hospital, Cincinnati 29, Ohio.)

Congenital biliary atresia is a developmental defect resulting in the complete exclusion of bile from the intestinal tract. The resultant severe hepatic damage produces many clinical abnormalities and severe skeletal involvement.

Roentgenographically, 2 types of bone disease are seen: the first is indistinguishable from deprivation rickets, and the second may represent the effects of a combined vitamin A and vitamin D deficiency. In both, the bones are deficient in mineral content and are unusually fragile, fracturing with minimal trauma but healing uneventfully. The epiphyseal centers appear late and there is severe dwarfism.

The type of bone involvement that resembles rickets roentgenographically shows poorly mineralized bowed bones with a coarse trabecular pattern. The depth of the epiphyseal cartilage is increased, and the ends of the diaphyses are frayed, cupped, and widened. Coxa vara, genu valgum, triradiate pelvis, and other rachitic deformities are generally present.

The second type of bone abnormality is unlike that caused by any vitamin, mineral, or nutritional disturbance. Roentgen examination reveals only severely hypomineralized bones which have a ground glass appearance. The cortices are pencil-line thin and the medullary cavities are widened. Undertubulation of the diaphyses is a prominent feature, so that the long bones have a box-like rectangular conformation. The depth of the epiphyseal cartilage is normal or decreased, and the adjacent zone of provisional calcification is smooth, thin, and of the same density as the cortex of the shaft. There is no bowing of bone and no joint abnormalities are seen.

The embryology, pathogenesis, diagnosis and treatment of the biliary defect is discussed. The underlying pathogenesis of the bone abnormalities is not clear. Two cases reports are presented and several roentgenograms are reproduced illustrating some of the bony manifestations.—*Donald N. Dysart, M.D.*

Blood and Lymph System

Epstein, Bernard S., and Epstein, Joseph A. Visualization of the basilar, cerebellar, and vertebral arteries during carotid cerebral angiography. *Radiology*, Nov., 1956, *67*, 738–741. (Address: B. S. Epstein, The Long Island Jewish Hospital, 270–05 76th Ave., New Hyde Park, N. Y.)

The basilar and cerebellar arteries are seldom visualized during carotid angiography. Retrograde

flow of contrast medium during percutaneous carotid angiography may occur when thrombosis of the internal carotid artery is present and result in visualization of the vertebral, basilar and cerebellar arteries. Occasionally the posterior communicating artery may be of sufficient caliber to permit flow of contrast medium into the superior cerebellar artery. Three cases are reported in which the arterial structures in the posterior cranial fossa were visualized during the course of percutaneous carotid angiography. In 1 case this was incident to thrombosis of the internal carotid artery. In the remaining 2 cases, the contrast medium traversed the posterior communicating artery to enter the superior cerebellar and basilar arteries.—*Harold C. Hamilton, M.D.*

Das, A., and Basu, A. K. Portal hypertension due to extrahepatic obstruction. *Brit. M. J.*, Feb., 1956, *1*, 325–328. (From: Nilratan Sircar Medical College and Hospital, Calcutta, India.)

Portal hypertension may be due to intrahepatic or extrahepatic causes. Among the latter, the more important recognized etiologic factors may be congenital or acquired stenosis of the portal system of veins; compression by tumors, cysts or cicatrix; thrombosis due to inflammation or traumatic causes; and, lastly, so-called cavernomatous transformation of the portal vein. Extrahepatic obstruction of the portal venous system of this type may produce the syndrome of splenic anemia with recurrent attacks of hematemesis as its chief symptom. So far, the exact nature and site of the obstruction could not be determined by clinical investigation; only at necropsy, or sometimes at operation, was this possible.

It is now realized that, in a fair number of cases of splenic anemia syndrome with hematemesis and melena as their chief features, the cause of the portal hypertension is some form of mechanical obstruction in the portal system of veins outside the liver. In the course of their investigations on splenomegalies of different types the authors found splenoportal venography a valuable method of accurately visualizing the portal system of veins.

Four cases of extrahepatic obstruction of the portal system with repeated severe hematemesis and melena were described. Two were due to cavernomatous transformation of the portal vein and the other two were caused by chronic inflammatory pancreatic masses.

The sites of obstruction and their possible nature were well demonstrated by splenoportal venography. The findings were confirmed in 1 case at necropsy and in the other 2 cases at operation.—*Barbara Thompson, M.D.*

Reedy, William J., Koszewski, Bohdan, and Murphy, Paul. Evaluation of aortic occlusion by aortography. *Ann. Int. Med.*, Feb., 1956, *44*, 283–291. (From: Departments of Medicine and Radiology, Creighton University School of Medicine and Creighton Memorial St. Joseph's Hospital, Omaha, Nebr.)

The authors' technique of puncture, injection and rapid filming of the aorta and its major branches as a safe and essential preoperative localizing and diagnostic study is presented in brief form.

Five conditions causing dilatation and tortuosity of the low abdominal aorta such as the Leriche syndrome (chronic low aortic or aorto-iliac obstruction), a Goldblatt kidney, a stenosis of the right common femoral artery, and an extrarenal tumor revealed by an abnormal nephrogram (retroperitoneal fibrosarcoma) are illustrated.

It is probable that the method will find utilization in the diagnosis of aneurysms of the splenic artery, abdominal calcifications, cysts, and neoplasms of the pancreas and liver, which are now not identifiable by conventional studies.

Aortography has become a necessary diagnostic method for the precise visualization of the location and extent of segmental obstruction of the aorta and its major branches.—*Joseph Bean, M.D.*

General

Stieve, F. E. Untersuchungen über das Wirkungsprinzip von Belichtungsautomaten für Röntgenaufnahmen. (Studies on the effective principle of automatic exposure meters for roentgenography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1956, *85*, 491–510. (From: Institut und Poliklinik für Physikalische Therapie und Röntgenologie der Universität, München, Germany.)

The author studied in great detail the behavior of 2 types of automatic intensitometers which are widely used in fluorography and photographic roentgenography. One type, the "Iontomat" (manufactured by Siemens-Reiniger in Erlangen, Germany) uses an ionization chamber to measure the dose required for a certain blackening of the film, while the other, the "Luminix" (manufactured by Koch and Sterzel in Essen, Germany) employs photoelectric cells to measure the luminosity of the screen. In practical use, the ionization chamber is placed in front of the film, while the electronic device measures either the light on a screen placed behind the film or the light on the transparent back intensifying screen. All density measurements were made on films of one emulsion (Kodak Regulix Em Nr. 31171). The intensifying screens were selected so as to insure photographic density characteristics which were practically independent of the applied

voltages used (50 to 120 kv.); for the "Luminix" intensitometer, the screen combination "Cawo Optima" and for the "Intomat" the combination "Siemens Saphir" were chosen as the best suited ones. Water phantoms of various thicknesses were used in the measurements. Individual phases of the investigations covered the dependence of the intensitometer's readings upon the tube voltage, and upon the thickness of the object, the effect of scattering and effects of rays falling obliquely upon the meters. Densities of films produced by radiations over a wide range of qualities were compared with the respective intensitometer readings. The ionometric device showed a certain dependence upon the quality of radiation, notably for voltages at the tube above 100 kv. This is probably mainly due to the properties of the ionization chamber. No dependence of the readings upon the thickness of the object could be detected. The photoelectric meter, which measures the light on the back intensifying screen, on the other hand, showed a dependence upon the thickness of the water phantom. This is probably due to the dependence of the filtering value of the front screen upon the wavelength. Both effects can be brought to a minimum by suitable selection of film and screen combinations. Despite these small errors in readings for various qualities of radiation both ionometric and electronic systems of intensitometers have, for all practical purposes, proved very useful.—*Otto Glasser, Ph.D.*

Fritz-Niggli, H. Neuere Ergebnisse der Strahlengenetik. (Newer results in radiation genetics.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1956, *85*, 265–273. (From: Strahlenbiologisches Laboratorium der Radiotherapeutischen Klinik des Kantonsspitals, Zürich, Switzerland.)

After a preliminary discussion of various concepts on genetics such as "Erbmasse," hereditary factors, genes, chromosomes, spontaneous and radiation-induced mutations, the author devotes the major part of the paper to a discussion of the laws of radiation genetics and describes a few of her own experiments on the biologic effects on *Drosophila melanogaster* of quanta produced with a 31 mev. betatron, as compared to equal doses of 180 kv. roentgen-photons. She comes to the conclusion that ionizing radiations produce the same mutations as occur naturally, but that they give rise to coarser changes of chromosome structure. Since mutations are irreversible injuries, even smallest doses may cause harm. At present no accurate statement on the kind of mutation produced can be made, and only extreme changes in ion-density show an influence upon the number of mutations produced. Germ cells show a different sensitivity to ionizing radiations at various stages of their formation. Germ cells of various ages also respond differently to ion-density and environmental changes. Oxygen tension and water content have some effect upon the number of mutations produced.—*Otto Glasser, Ph.D.*

RADIATION THERAPY

Burnett, Harry W., and Herbert, Earle A. The role of irradiation in the treatment of primary malignant lymphoma of the stomach. *Radiology*, Nov., 1956, *67*, 723–728. (Address: H. W. Burnett, New York Hospital, 525 East 68th St., New York 21, N. Y.)

The authors report the results of a study to evaluate the role of irradiation in the management of primary malignant lymphoma of the stomach. Twenty-seven cases of primary malignant lymphoma are reviewed as to treatment and end results. All patients were explored. Whenever possible, primary resection of the involved portion of the stomach was performed. Those patients showing evidence of residual disease were referred for supplementary irradiation.

Seven patients were treated by resection only because it was believed that the tumor was completely removed by surgery. Three of these, 42.8 per cent, lived more than ten years.

In 17 patients there was extension of the disease beyond the margins of resection. These patients were treated in essentially the same manner with 200 to 250 kv. roentgen rays with a half-value layer of 1.5 to 2 mm. of copper. Usually two anterior and two posterior portals were cross-fired at the level of the affected region. Tumor doses ranged from 1,600 r in thirty-seven days to 4,690 r in forty-nine days. Six of this group of 17 patients were alive at the end of five years, and 3 were still alive at seven years. Individual tumor sensitivity to irradiation and extent of disease apparently were deciding factors in survival times. A tumor dose of 3,000 to 3,500 r in about forty days is suggested as the optimal dose.

Three cases were considered unresectable, and only palliative procedures were employed. Survival times ranged from 2 to 5 months for this group.

The authors consider it probable that equally good results should be expected if, following biopsy, patients are treated by irradiation alone, without preliminary resection, since long-term survivals are obtained in patients with disease beyond the scope of resection.—*A. W. Sommer, M.D.*

RADIOISOTOPES

McConahey, William M., and Owen, Charles A., Jr. Studies of the inhibitory effect of l-triiodothyronine on thyroidal I^{131} uptake in euthyroid persons and patients with exophthalmic goiter. *J. Clin. Endocrinol. & Metabol.*, Nov., 1956, *16*, 1480–1486. (From: Section of Medicine, and Section of

Clinical Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

In daily doses of 3.5 to 17.5 micrograms, l-triiodothyronine administered to euthyroid subjects induced moderate, though often transient, inhibition of the 24 hour thyroidal uptake of I^{131} in most subjects. In daily doses of 25 to 140 micrograms it uniformly induced prompt inhibition of the 24 hour uptake; the larger the dose, the more rapid the inhibition.

There was no significant inhibition of the 24 hour thyroidal collection of I^{131} in 7 patients with exophthalmic goiter to whom l-triiodothyronine was administered.

Among normal subjects whose I^{131} uptake was depressed by l-triiodothyronine, the intramuscular injection of 5 units of thyrotropin caused the uptake to return to normal or above-normal levels. This observation supports the theory that l-triiodothyronine exerts its thyroid suppressive action by the inhibition of secretion of thyrotropin.—*R. Kenneth Loeffler, M.D.*

VAN MIERT, P. J., and FOWLER, J. F. The use of tantalum 182 in the treatment of early bladder carcinoma. *Brit. J. Radiol.*, Sept., *29*, 508–512. (From: Radiotherapy Department, Royal Victoria Infirmary, Newcastle upon Tyne, England.)

Methods available for treatment of bladder carcinoma are briefly considered. The unique potential advantage of interstitial irradiation—uniform and adequate dosage to the lesion-bearing area and reduced dosage to uninvolved bladder—is considered worthy of greater attention. The authors' method of using interstitial implantation of tantalum 182 wire is described with illustrative cases. Special equipment used in the implantations and physical principles governing uniformity of dosage in implantations are briefly discussed.—*John T. McLelland, M.D.*

BOND, V. P., EASTERDAY, O. D., STICKLEY, E. E., and ROBERTSON, J. S. The relative biological effectiveness of thermal neutrons and of the heavy particles from the B^{10} (n, α) Li^7 reaction for acute effects in the mouse. *Radiology*, Nov., 1956, *67*, 650–664. (Address: V. P. Bond, Medical Department, Brookhaven National Laboratory, Upton, L. I., N. Y.)

Although the relative biological effectiveness of alpha or of heavier ionizing particles has been extensively studied in microorganisms, only a few attempts have been made to determine the RBE of such particles in the mammal. This is due principally to the technical difficulties inherent in obtaining total body or large-volume irradiation of the intact animal with heavy particles with a range in tissue of the order of a few microns. The most direct approach, *i.e.*, injection of alpha emitters into the intact animal, is not completely satisfactory for a number of reasons. It is possible, by delivering total-body thermal neutron radiation to mammals previously injected with a capture element such as boron or lithium, to obtain irradiation of the tissues with the heavy recoil particles liberated instantaneously in the capture process. The investigation reported in this article was carried out in order to determine the apparent RBE of the heavy particles thus liberated for acute effects in the mouse.

In this study, single whole-body doses of thermal neutron radiation were delivered to female mice injected intravenously five minutes previously with boron in the form of borax. The biological endpoint studied was the degree of spleen and thymus weight depression when the animals were sacrificed three and one half days after exposure. The rem dose rates from slow neutron irradiation and from the heavy particles from slow neutron capture by boron (alpha particle and recoil lithium nucleus) were found to be completely additive. The average rep dose from thermal neutrons alone and from boron capture was calculated, assuming the mouse to be a "thin foil," from the estimated tissue boron content, the slow neutron capture cross-section for boron, the measured slow neutron flux at the proximal skin surface, and the energy release per neutron capture. The effectiveness of thermal neutrons alone, relative to Co^{60} gamma radiation (apparent RBE) was calculated to be 3.8. The apparent RBE of the heavy particles from slow neutron capture by boron was found to be approximately 1.6. This value was increased to 2.5 if the energy liberated by the alpha particle only was considered in the rep determination. —*A. Ralph Watson, M.D.*

FINKEL, MIRIAM P. Relative biological effectiveness of internal emitters. *Radiology*, Nov., 1956, *67*, 665–672. (Address: Argonne National Laboratory, Lemont, Ill.)

The acute and chronic toxicity of internally deposited radioisotopes is being studied in CFI female mice under standardized conditions. Data accumulated in such studies make possible an evaluation of the realtive biological effectiveness (RBE) of different radioisotopes according to a number of criteria. The isotopes included in this study are Ra^{226}, Pu^{239}, Po^{210}, U^{233}, U^{232}, Th^{228}, Ru^{106}, Sr^{90}, Sr^{89}, Y^{90}, P^{32}, and Ca^{45}.

The alpha-emitting isotopes tested are approximately twenty times as effective as radium 226 (on the basis of dose injected per unit weight) in killing half of the population in twenty to thirty days. This result is not readily explainable in terms of particle energy, physical half-life, biological half-

time, or tissue distribution. The beta-emitting isotopes tested are less potent killing agents at acutely lethal levels than Ra^{226}. Their relative effectiveness can be interpreted in large part on the basis of energy and half-life; those with relatively long half-lives are approximately twice as lethal as those with very short half-lives and there appears to be a direct relationship between energy and lethality. The distribution of the radioisotopes within the body and their retention seem to be relatively unimportant when acute lethality is the criterion of effect.

During the first four hundred and twenty-five days there was a perceptible increase in mortality rate with lymphoid tumors among the animals that received appropriate doses of Pu^{239}, Ra^{226}, Sr^{89}, Sr^{90}, and Ca^{45} and a pronounced increase among those that received Po^{210}, P^{32}, and Y^{90}. Tentative figures for relative effectiveness in inducing malignant bone tumors based on an average rate of 10 deaths with bone tumors per twenty-five days per 100 animals are 20(Pu^{239}); 1(Ra^{226}); 0.2(Sr^{90}); 0.1(Sr^{89}); 0.05 (Ca^{45}).—*Harold C. Hamilton, M.D.*

Riley, E. F., Evans, T. C., Rhody, R. B., Leinfelder, P. J., and Richards, R. D. The relative biological effectiveness of fast-neutron and x-radiation; survival and cataract studies of Swiss mice. *Radiology*, Nov., 1956, *67*, 673–685. (Address: E. F. Riley, Radiation Research Laboratories, State University of Iowa College of Medicine, Iowa City, Iowa.)

The relative biological effectiveness (RBE) of fast-neutron and roentgen radiations are of importance to persons responsible for radiation safety measures, as well as those interested in the mechanisms of radiobiological actions. In order to establish acceptable tolerance limits for neutron radiation the most unfavorable effectiveness ratios must be considered. Since earlier studies indicated that lens damage was one of the more critical biological effects of low-level neutron irradiation, further studies of the relative cataractogenic effectiveness of fast-neutron and/or gamma radiations were undertaken. The biological unit of exposure, the 30-day LD_{50}, was also studied. This paper summarizes the observations of these authors on survival and cataract development after single exposures to several neutron sources as compared with observations after roentgen irradiations.

The methods and techniques of irradiation of mice of an albino Swiss stock are described and the results and evaluations are reported. Damage to the lenses was best evaluated one year post-irradiation. In general, it was found that the higher-energy neutron radiations are biologically less effective, both for lethality and cataractogenesis, than the lower energy neutron radiations. Also, the CD_{50} (cataractogenic dose 50) is greater than the LD_{50} following exposure to roentgen radiation, while for neutron radiations the CD_{50} is less than the LD_{50}. Death of the experimental animals occurred sooner after neutron irradiation than after roentgen irradiation. A study of the cataract curves showed that the chances for recovery after roentgen irradiation were greater than after neutron irradiation. A rather long plateau was found on the roentgen cataract curve extending from about 100 to 500 r. Within this range of exposure, damage to the lens appears to be limited and, at about six to eight months after irradiation, the lens seems to "recover."

Several tables and figures are presented which illustrate the findings.—*Donald N. Dysart, M.D.*

Upton, A. C., Christenberry, K. W., Melville, G. S., Furth, J., and Hurst, G. S. The relative biological effectiveness of neutrons, x-rays, and gamma rays for the production of lens opacities: Observations on mice, rats, guinea-pigs, and rabbits. *Radiology*, Nov., 1956, *67*, 686–696. (Address: A. C. Upton, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.)

The authors report the results of studies to obtain quantitative information about the relative biological effectiveness (RBE) of neutrons, roentgen rays, and gamma rays for the production of lens opacities in several species of mammals.

Mice, rats, and guinea pigs were exposed in the cyclotrons to neutrons having a mean effective energy of 1–2 mev. obtained by the Be(p.n) reaction. After irradiation, the survivors were examined periodically for lens opacities with a Zeiss-Opton slit lamp. For purposes of comparison, animals of corresponding age, sex, species, and strain were exposed to 250 kv. peak roentgen rays. RF mice were also exposed to Co^{60} gamma rays. In most instances doses of irradiation were administered in a single brief exposure of the whole body. The radiosensitivity of the lens varied appreciably with species; the mouse, rat, guinea pig, and rabbit exhibiting decreasing sensitivity in the order listed, all being presumably more sensitive than man. With fractionation of neutron or gamma irradiation, there was only slight reduction in dose effectiveness at low dose levels in mice.

For the production of cataracts in mice, rats, and guinea pigs, cyclotron neutrons of 1 to 2 mev. mean effective energy, administered at high intensity, were 2 to 4 times as effective as 250 kv. peak roentgen rays and 3 to 4 times as effective as 1.2 mev. gamma rays. Fission neutrons from an experimental nuclear detonation and thermal neutrons had a similar cataractogenic effectiveness in mice.

The RBE of fast neutrons of 2 to 3 mev. mean energy administered at relatively low intensities was

approximately 9 for induction of mild opacities in mice and appeared to be greater than 9 for the production of threshold lens damage.—*A. W. Sommer, M.D.*

MOOS, WALTER S., FULLER, JOHN B., HENDERSON, WALTER J., and HARVEY, ROGER A. The effects of conventional and high-energy x-rays and electrons in fractionated dosage on rats. *Radiology*, Nov., 1956, *67*, 697–703. (Address: W. S. Moos, 840 S. Wood St., Chicago 12, Ill.)

The authors have conducted experiments in order to establish the degree to which fractionated roentgen ray and electron dosages influence the survival and other biological activities of rats, in comparison to equal amounts of ionizing radiation of lower energy. Survival studies showed that there was no qualitatively different reaction in these animals when they were irradiated with fractionated dosages of 400 kv. and 22 mev. roentgen rays.

The relative biological effectiveness of the two energies of ionizing radiation was of the order of 0.56 to 0.75. The lower RBE factor at smaller daily dosages (50 and 100 r/day) is in accordance with similar findings by Quastler and Lanzl, who irradiated mice with divided doses of betatron roentgen rays.

Irradiation of rats with 20 mev. electrons produced results almost identical with those obtained with 22 mev. roentgen rays. The RBE value also remained unchanged. No significant variation of the RBE value was obtained by treating the animals at a

$$\frac{\text{150 r/day (400 kv. roentgen rays)}}{\text{250 r/day (22 mev. roentgen or 20 mev. electrons)}} = 0.6$$

or at 1:1 dosage ratio.

It was found that weight loss variations can also be attributed only to a quantitatively different process. Again the RBE factor approximates closely a 0.6–0.7 value.

Gross pathologic examination of the rats gave no clues suggesting any other damages than those generally observed in mammals exposed to low energy roentgen rays.—*A. Ralph Watson, M.D.*

HEVESY, G. C. Radioactive tracers in radiobiological studies; The Thirty-Sixth Silvanus Thompson Memorial Lecture. *Brit. J. Radiol.*, Sept., 1956, *29*, 465–477. (From: Institutet für Organisk Kemi och Biokemi, Stockholms Hogskola, Sweden.)

In an excellent presentation of a somewhat complicated assortment of experimental data, the author reviews, at length, pathochemical changes resulting from irradiation, particularly as reflected in altered desoxyribonucleic acid metabolism. While so doing, he illustrates the important role radioactive tracers, such as P^{32}, C^{14} and Fe^{59} have played in radiobiologic studies.—*John T. McLelland, M.D.*

WILSON, C. W. The effect of x-rays on the uptake of phosphorus 32 by the knee joint and tibia of six-week-old mice: Relation of depression of uptake to x-ray dose. *Brit. J. Radiol.*, Oct., 1956, *29*, 571–573. (From: Physics Department, Westminster Hospital, London, S.W. 1, England.)

The depression of P^{32} uptake in the knee joint and tibia of six-week-old mice following roentgen irradiation with 1,000 r to 2,000 r is plotted against time following irradiation. Maximum depression is produced in the knee joint about four to eight weeks after irradiation. In the range of dosages tested, the relationship between maximal depression and dosage administered is linear. The author suggests that this basic information may be profitably used examining the effects of such factors as oxygen tension and administered chemical substances.—*John T. McLelland, M.D.*